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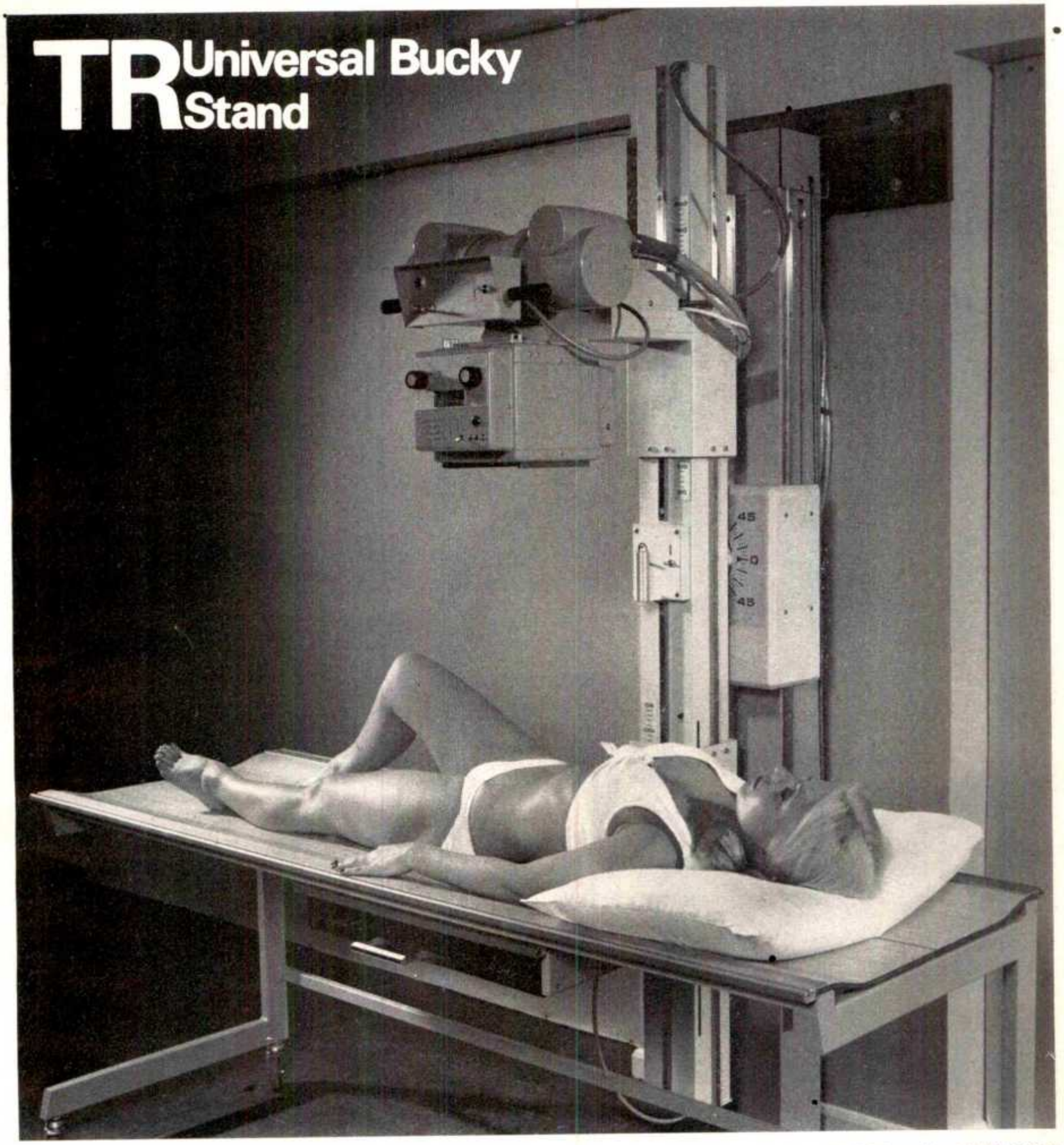

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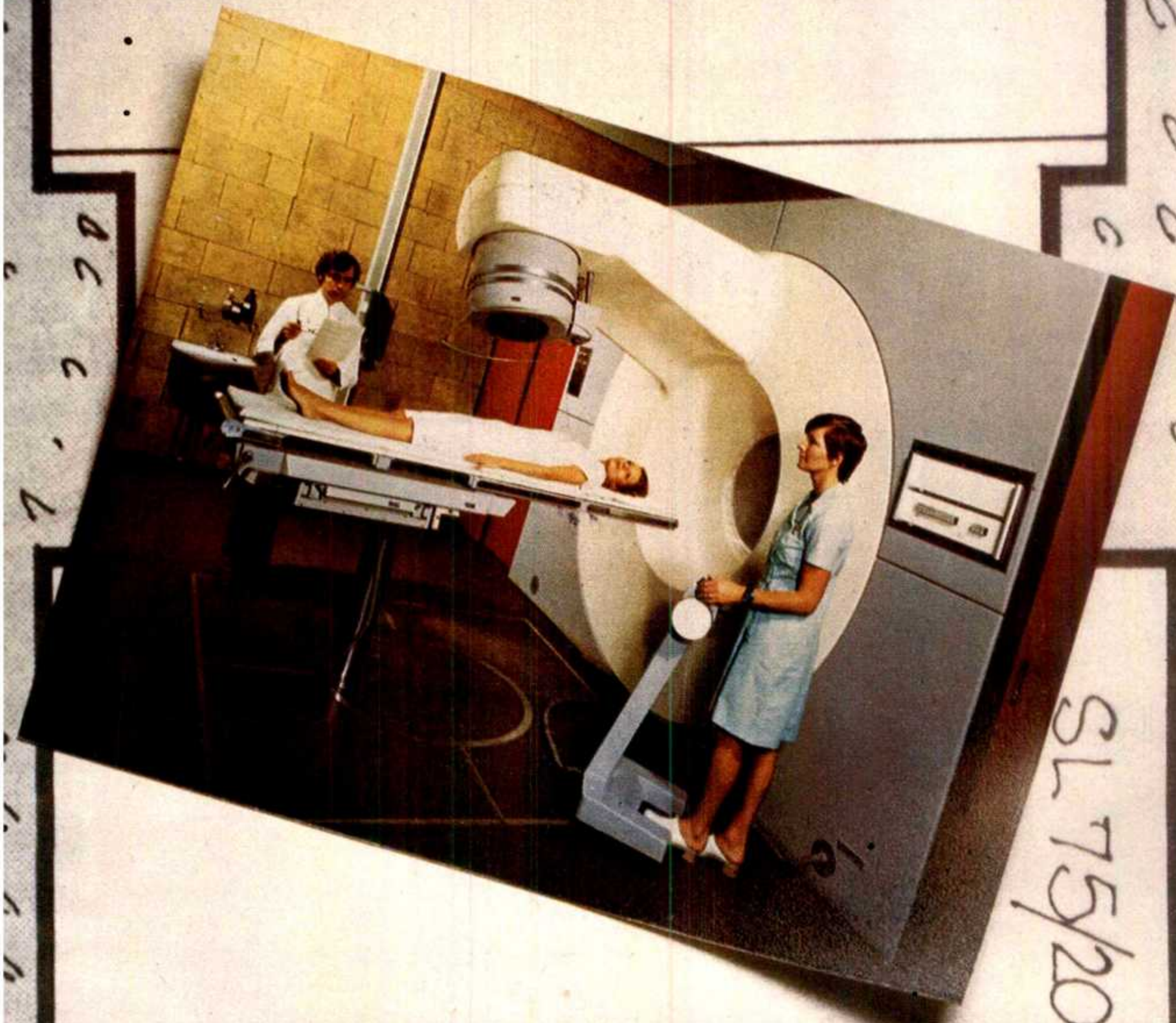

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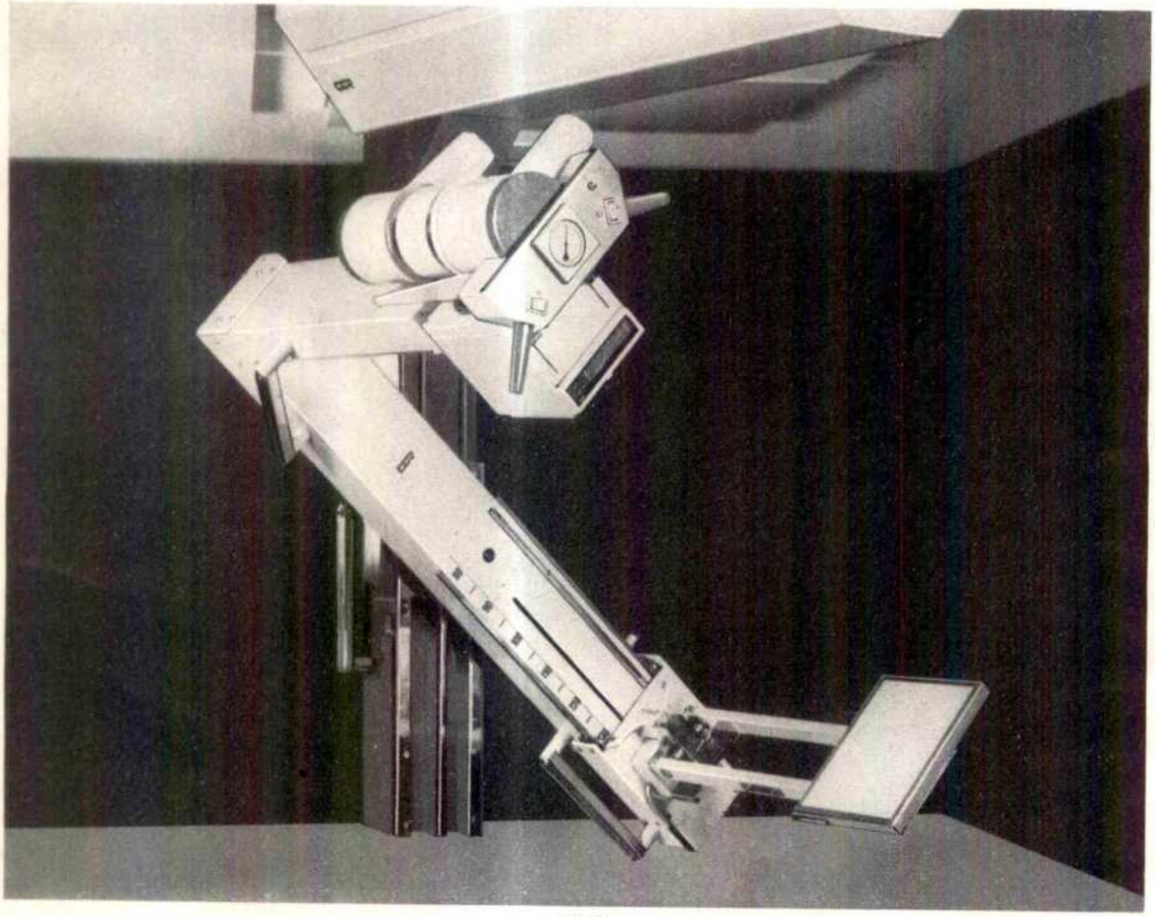

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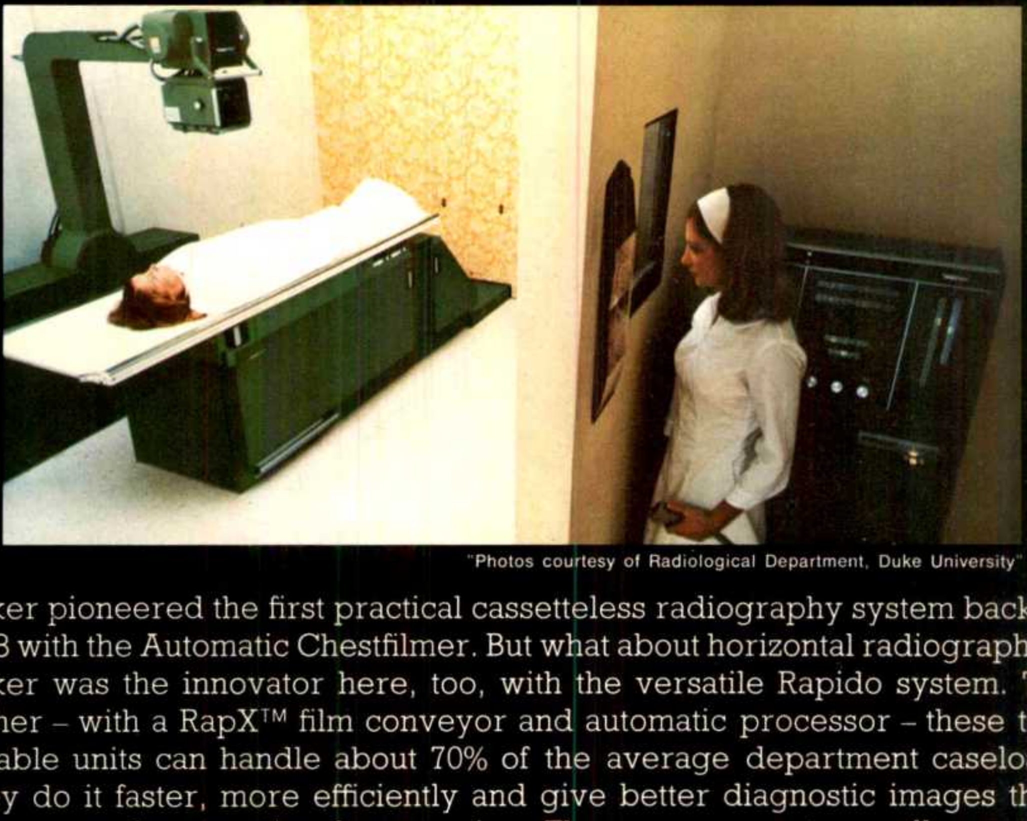

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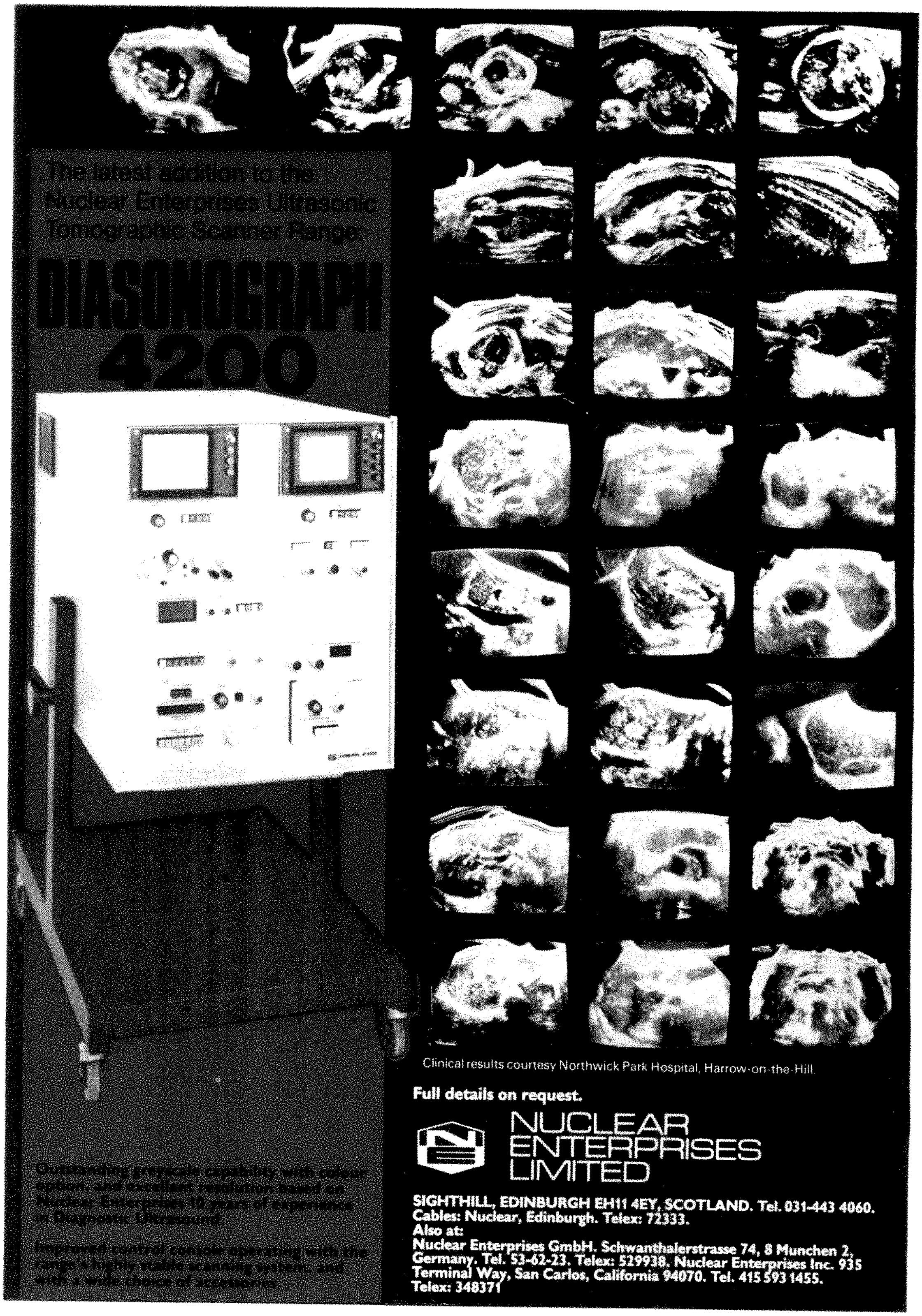

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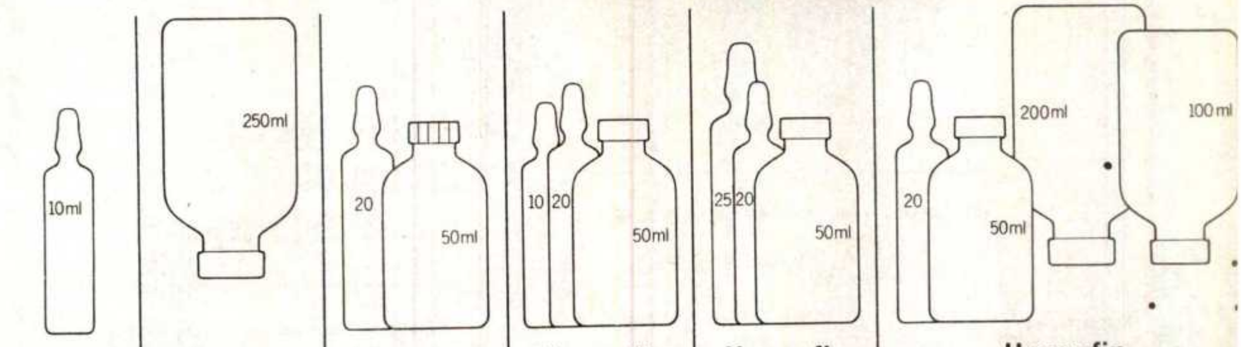

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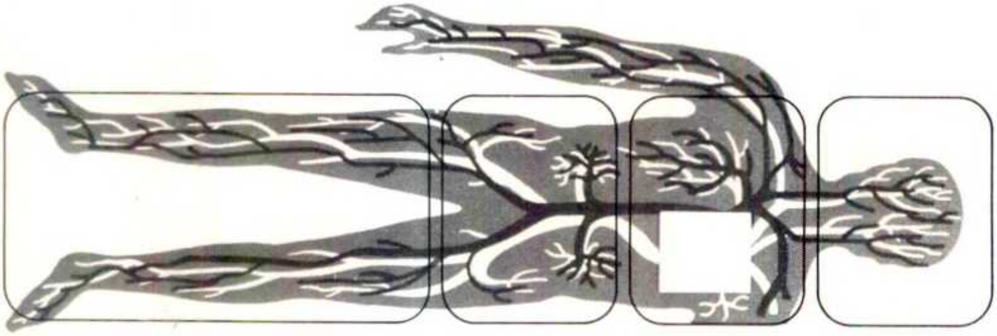

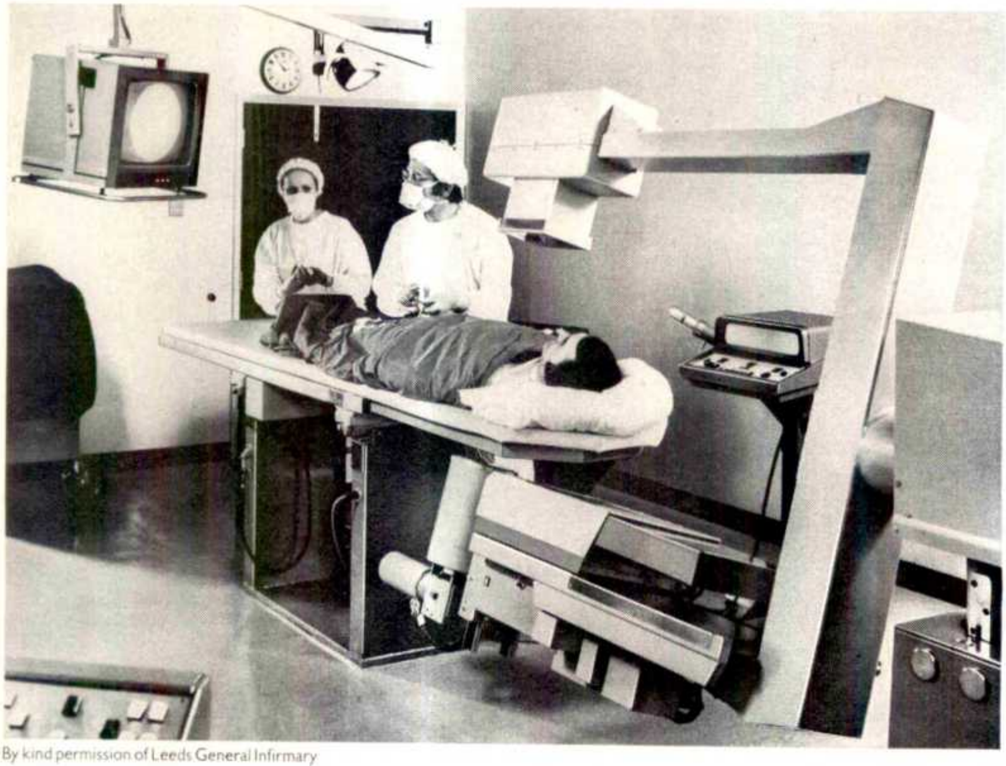

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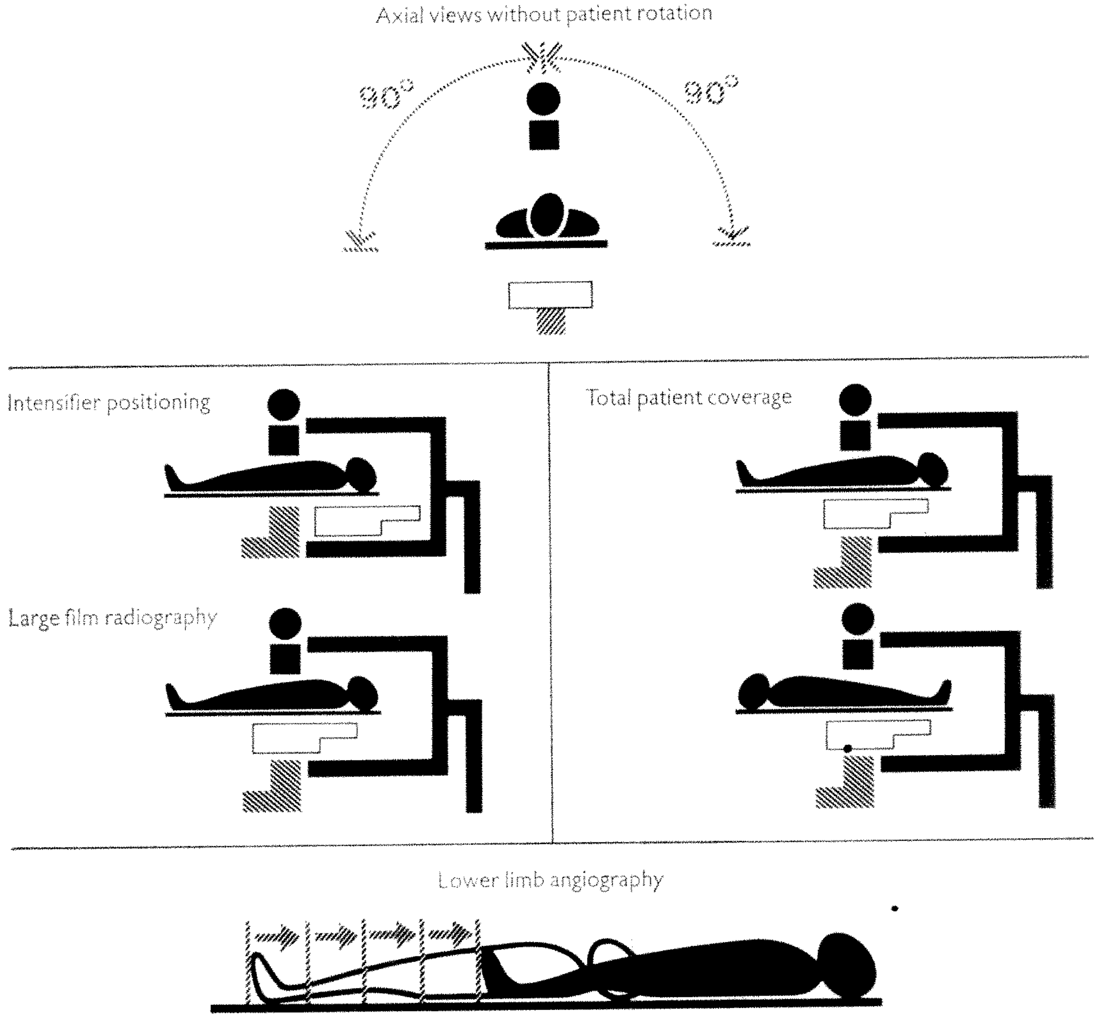

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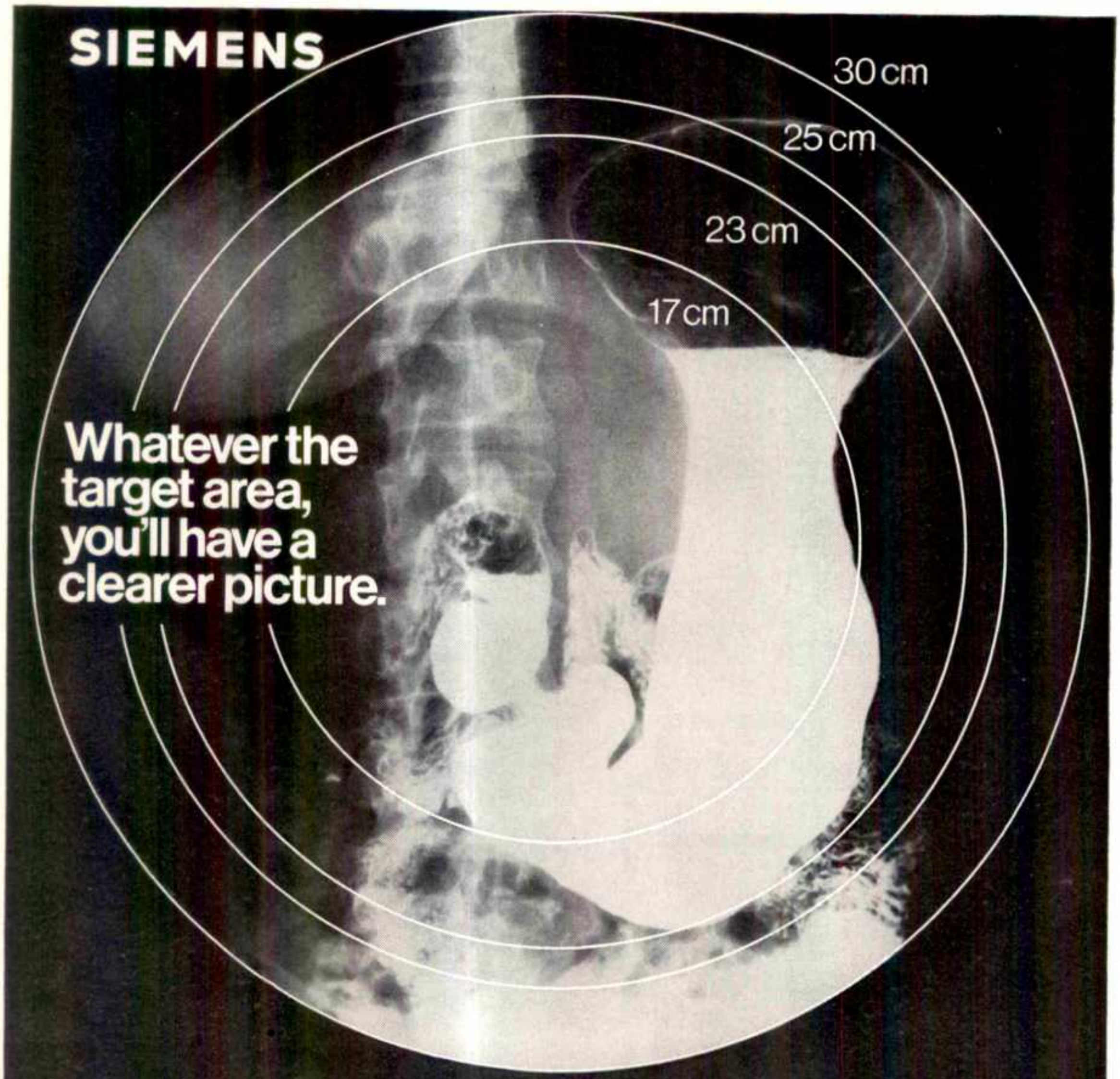

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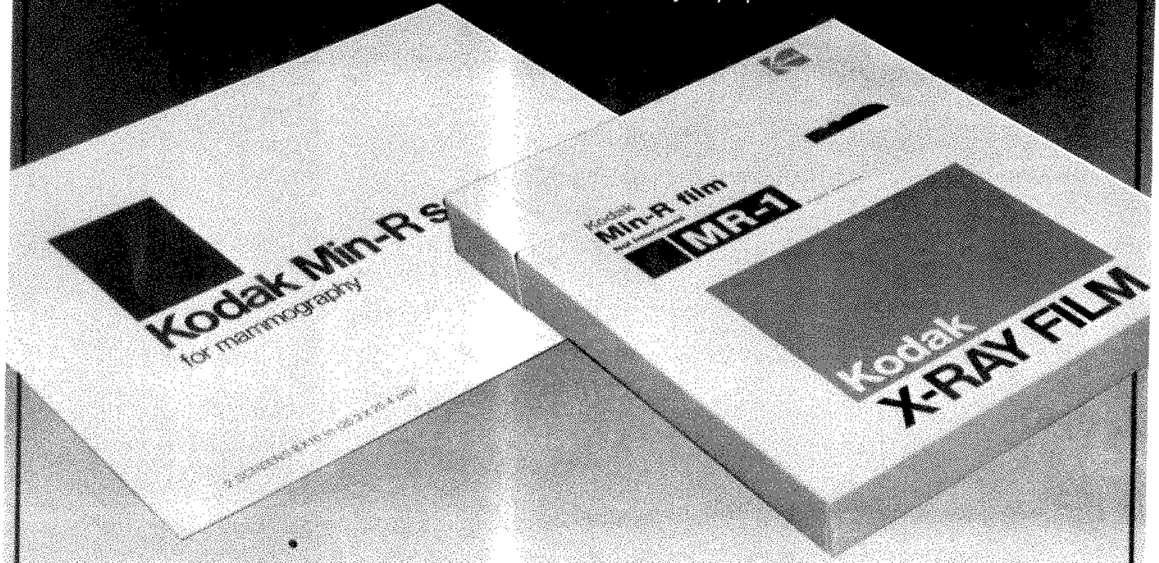

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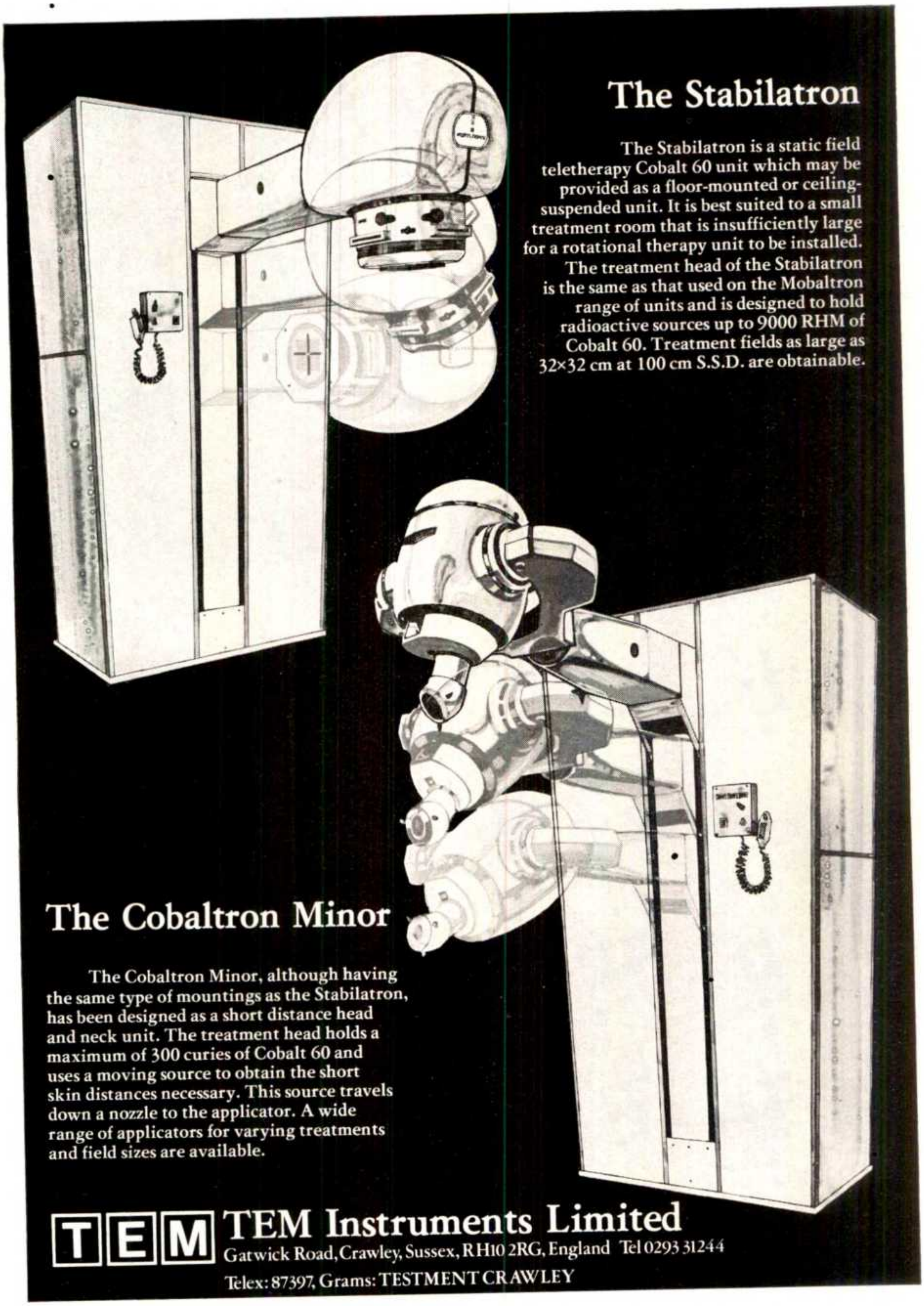

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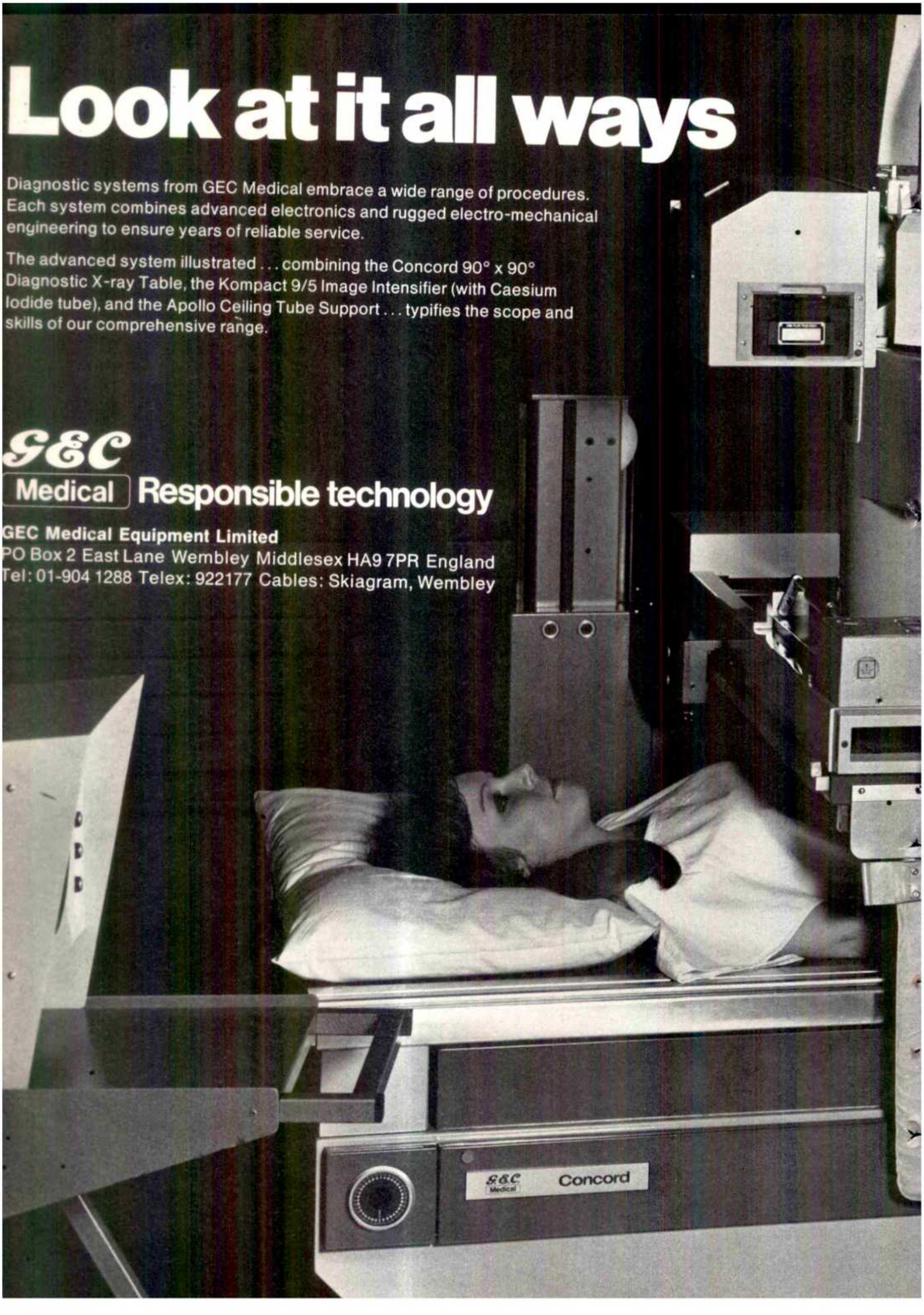

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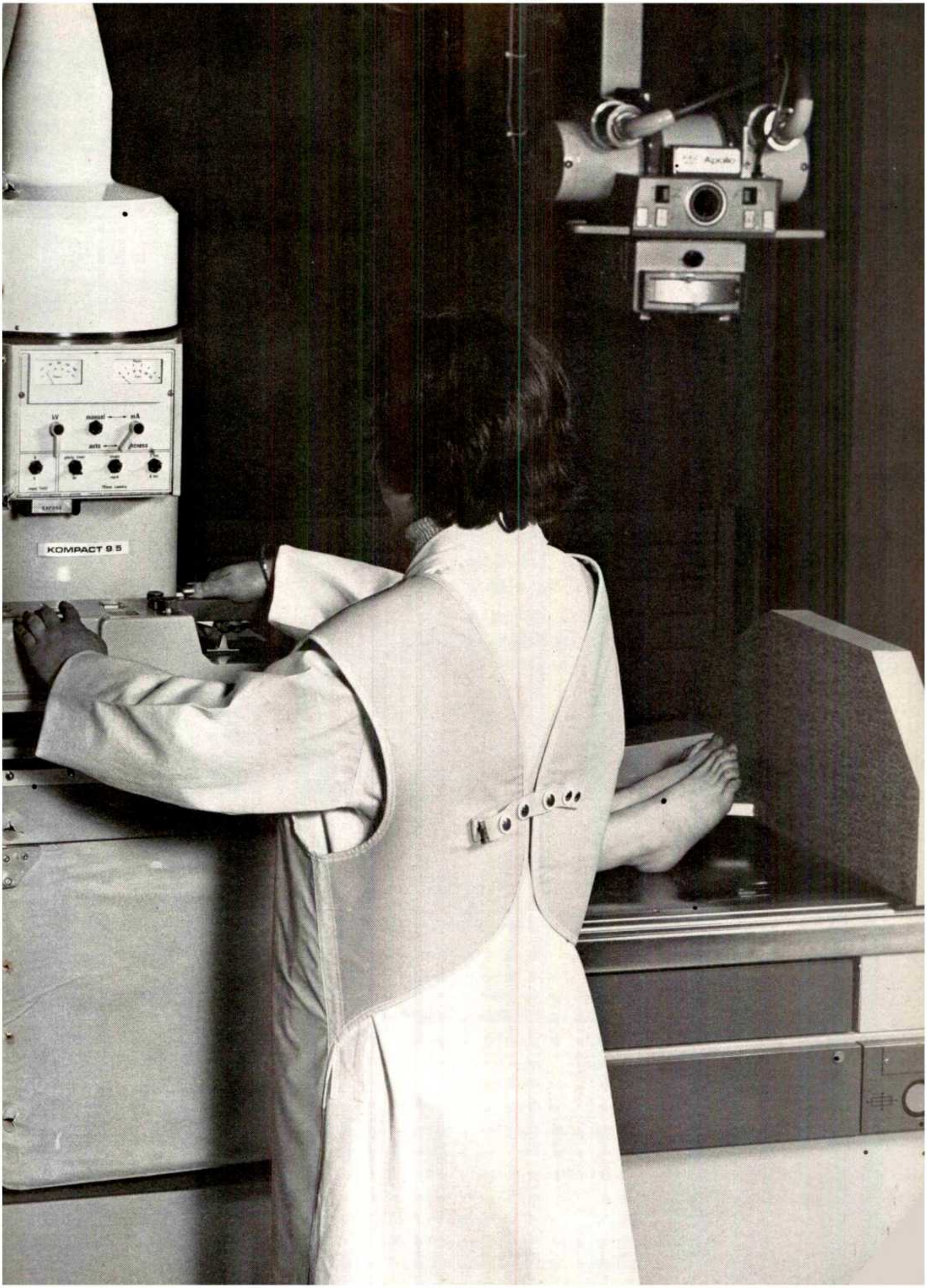
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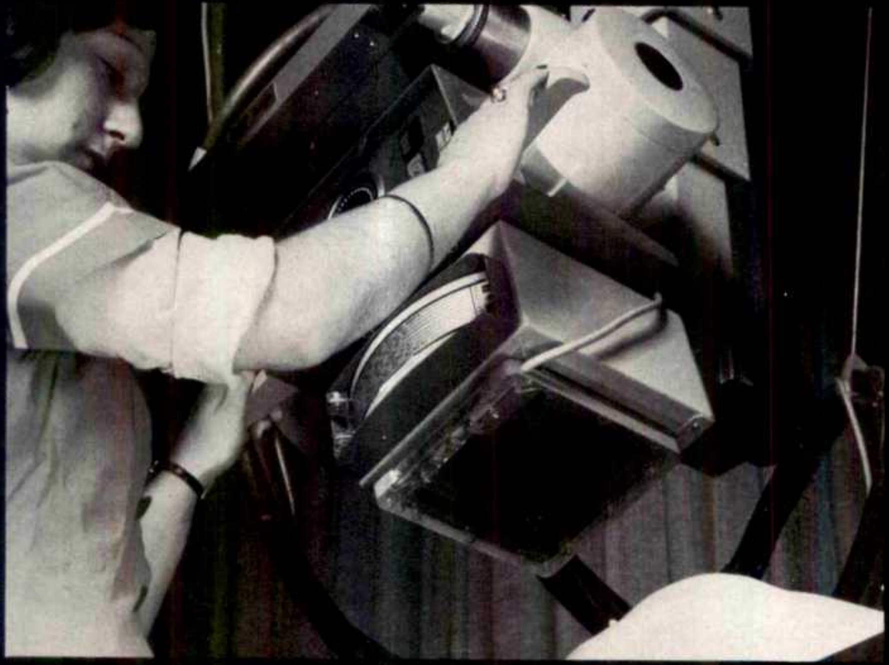

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- R. F. Mould
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- C. Gregory
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The British Journal of Radiology

Radiology now

Malignancies following low radiation exposures in man*

It is very hard to estimate the risk of malignancy entailed in exposure to low doses of ionizing radiation. The risk from higher doses (100 rad or more) can now be estimated approximately from several sources of epidemiological evidence, both for exposure of the whole body and for that of a number of organs or tissues. Many of these sources are imperfect in some respects, often involving inadequate periods of follow-up, deficient control data, uncertainty of dose at the site of interest or of RBE for exposures to radiation of high linear energy transfer (LET), or gross statistical imprecision if only small excess numbers of tumours are observed. Together, however, these data are beginning to justify estimates of the frequencies with which malignancies are induced in man in various tissues by moderately high absorbed doses, often delivered at high dose rate.

Until recently there was little information on the frequencies of tumour induction by doses of only a few rad, and no reliable basis for inferring this frequency from that observed at considerably higher doses. Moreover, the great variability in the frequency of tumour induction by radiation in different animal species, and even in different strains of the same species, prevents any quantitative inferences being applied directly to man.

Three pieces of evidence now appear to indicate the induction of malignancies in man by absorbed doses of less than 10 rad.

Leukaemia following atomic bomb exposures

Both in Hiroshima and in Nagasaki, the death rate from leukaemia for the period October 1950 to December 1972 exceeds that expected on the basis of Japanese national rates (Table I), even for the group of people estimated to have been exposed to doses of less than 10 rad (tissue kerma in free air, according to the T65, or tentative 1965, dose estimate, Moriyama and Kato, 1973). For Hiroshima, about 20 per cent of the total dose is estimated to have been due to neutrons (Jablon and Kato, 1971), so that it is difficult to evaluate the equivalent total dose of low LET radiation, particularly at these low doses where RBE may be high. The increase in death rate, however, although small, is also significant in Nagasaki where no significant neutron exposure occurred, and where the mean gamma dose was again small, with an average of 4 rad in 60 per cent of the group and less than 1 rad in the remainder. The mean absorbed doses in bone marrow are under review (Jones *et al.*, 1975) but are unlikely to have been higher than these kerma estimates.

The use of Japanese national rates as a basis for comparison could be questioned if there were regional differences in leukaemia incidence, but it may be noted (Table I) that no increase in mortality ratio

TABLE I

MORTALITY RATIOS FOR LEUKAEMIA RELATIVE TO JAPANESE NATIONAL STATISTICS (Moriyama and Kato, 1973)

Males and females, all ages, deaths 1950–1972 (with confidence limits, at 10 and 90 percentile points)

Group	Exposed at 0–9 rad	Not in city
Hiroshima	1·48 (1·18–1·84)*	0·88 (0·54–1·35)
Nagasaki	1·78 (1·11–2·63)	1·11 (0·48–2·21)

Kerma estimates (in free air) for 0–9 rad groups (Jablon and Kato, 1971)

Hiroshima	29,934 persons at less than 1 rad + 13,787 at mean dose 2·9 rad (gamma) + 0·8 rad (neutron)
Nagasaki	4,699 persons at less than 1 rad + 6,705 at mean dose 4·0 rad (gamma) + 0·0 rad (neutron)

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*Reprints: Sir E. E. Pochin, National Radiological Protection Board, Harwell, Didcot, Oxfordshire OX11 0RQ.

is observed in those residents who were not in the city at the time of bombing, returning to it shortly after.

Thyroid cancers following scalp irradiation in childhood

Modan *et al.* (1974) report the development of a significantly greater number of cancers of the head and neck in children whose scalps had been irradiated for tinea capitis, than in two matched control groups. Twelve thyroid tumours diagnosed as being malignant occurred within 12 to 24 years of irradiation of 10,902 children. Two such tumours were recorded in 10,902 non-irradiated subjects matched for age, sex, country of origin and date of immigration. One was recorded in a second control group of 5,496 unirradiated siblings of the irradiated children, matched for age to within five years. The staff who searched records for tumour incidence were unaware of whether named subjects were from irradiated or control groups.

The scalp was irradiated on separate days by five fields at an air dose of 350 to 400 R. Detailed studies on a phantom (Werner *et al.*, 1968) showed that the thyroid should have received a total average absorbed dose of 6·2 to 7·4 rad. On this basis, the rate of tumour induction per rad is given by

$$\frac{(12-2)}{10{,}902\times 6{\cdot}5}=(140\pm50)\ 10^{-6}\text{ cases per rad.}$$

It will be noted that this is consistent with the rates per rad observed by Hempelmann (1968) in children following estimated mean doses to the thyroid of about 350 rad. Modan and his colleagues emphasize that the thyroid exposures may have been greater than those estimated in the phantom if a constant head position was not maintained during the therapy. It seems unlikely, however, that mean thyroid doses would have greatly exceeded those estimated, and probable therefore that thyroid malignancies may be induced occasionally in children at doses of less than 10 rad.

Malignancies following fetal irradiation

The earliest indication that low doses might induce malignancies came from evidence that mothers of children with leukaemia had more frequently had diagnostic X-ray examinations of the pelvis during the relevant pregnancy than mothers of normal children (Stewart *et al.*, 1956). It was later found that the frequency with which malignancies developed within the first ten years of life was increased, probably by about 40 per cent in children exposed to diagnostic X rays while *in utero* (McMahon, 1962), the increase affecting focal tumours, particularly of the central nervous system, as well as leukaemia. No accurate estimate could be obtained of the risk of tumour induction per rad, since no direct information was available of the absorbed dose in the fetus per film or per examination. From a study of a number of estimates of fetal dose in the period 1946 to 1957 in British publications, the incidences reported by Stewart and Kneale (1970) were considered by UNSCEAR (1972) to correspond to fetal absorbed doses varying in individual cases from 0·2 to 20 rad, with a mean of less than 2 rad, and to a risk of fatal malignancy of about $23\cdot10^{-6}$ per rad per year to age 10.

The inference that the radiation caused malignancies was, however, questioned at first. For example, a sub-group of mothers might have been more frequently X-rayed than mothers in the control group because of hereditary abnormalities, *e.g.* of the pelvis, and this sub-group might have a preponderance of children who developed malignant disease as a result of some associated congenital abnormality.

Such a source of bias now appears to be excluded, however, by two considerations. Firstly, Stewart and Kneale (1970) showed that the likelihood of subsequent malignancy per examination increased about linearly with the number of films used in the examination, where this number was known. And secondly, Mole (1974) has shown from analysis of the data published by Stewart that mothers have pelvic X-ray examinations much more frequently (in 55 per cent of cases) during twin pregnancies than during singleton pregnancies (when only 10 per cent of mothers are X-rayed). Despite this, the excess frequency of malignancies in twins who were irradiated *in utero* is no higher than that in singletons so irradiated. Therefore the factors which called for a greater frequency of pelvic X rays, at least in this type of pregnancy, do not appear to be associated with an increase in childhood malignancies. For leukaemia, the excess rate per intra-uterine examination was $(118\pm16)10^{-6}$ in singletons and $(143\pm46)10^{-6}$ in twins. For focal cancers the result was similar, the excess rates per examination being $(124\pm17)10^{-6}$ in singletons and $(114\pm53)10^{-6}$ in twins.

It now appears likely, therefore, that absorbed doses of only a few rads in the fetus may induce malignancies of various types, and that the risk per rad of induction of such tumours does not differ greatly from that inferred for whole body exposures of adults at considerably higher absorbed doses (UNSCEAR, 1972).

DISCUSSION

These indications of the induction of malignancies in man at doses of less than 10 rad do not in themselves give any adequate basis for the various estimates required for protection purposes, of the risks of occupational exposures at corresponding dose levels of the whole body, or of various organs in the adult. Still less do they justify inferences as to the effects of exposure of populations at mean annual doses of only a few millirad in excess of background from various environmental sources.

They do, however, add weight to the indication of tumour induction from fractionated exposures, for example from repeated fluoroscopies, in which the total doses are high but individual fractions are low, and so to the possibility of obtaining estimates of low dose effect from them.

They also suggest that no very large "protraction factor" may be needed in reducing dose estimates per rad derived from high doses to infer those applicable at low doses. This conclusion already appeared likely for genetic effects and for changes induced in cell cultures (both for low LET radiation and even more so for high LET), where primary effects of radiation appear to involve changes induced in single cells (Kellerer and Rossi, 1971). For cancer induction, however, where microdosimetric considerations suggest the initial involvement of groups of cells (Rossi and Kellerer, 1972) the expectation is less clear. Direct evidence that occasional malignancies may in certain circumstances be induced in man at absorbed doses of only a few rad, however, indicate the need for continued caution in determining protection criteria in this respect also.

E. E. POCHIN

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Book review

A Handbook of Radiography. By J. A. Ross and R. W. Galloway, 4th edition, pp. 275 + index, 1976 (H. K. Lewis & Co.), £7·00.

This is a neat little hardback pocket-book intended for D.S.R. radiography students and student radiologists.

The fourth edition has been brought up to date with the addition of simple descriptions of new techniques such as ultrasonics and electron radiography, but to try to explain computerized axial scanning in half a page seems to be over ambitious.

As an attempt to cover the whole of the D.S.R. syllabus in one small volume the book fails. However, Chapter 2 on radiation hazards and the short descriptions of specialized techniques could be useful for reference.

Chapters 4–7 on radiographic positioning contain some excellent line-drawings, but in an attempt at brevity sometimes omit accurate centering points or special extra views which are the very things which student radiographers are most likely to need to look up.

As a short manual of practical radiography the reviewer feels that this book could be useful to radiologists studying for Part I of the F.R.C.R. and possibly as a revision for student radiographers.

JENNIFER RICHMOND.

1976, *British Journal of Radiology*, *49*, 580–582

Fetal cervical hypertension in breech presentation

By J. G. B. Russell and Margaret R. C. Aird

St. Mary's Hospital, Manchester 13

(*Received April, 1975*)

ABSTRACT

A review has been made of Down's syndrome patients who were radiographed as fetuses and the majority were found to be in abnormal postures, often "star gazing". Further review of "star gazing" fetuses showed that two of eight were normal and the rest were abnormal. Hypotonia was a frequent association.

The causes of a hyperextended neck in a breech presentation (a "stargazing fetus") were listed by Behrman (1962) who found 14 associated factors. He believed fetal hypertonicity was the usual cause. The finding of this posture is important because cervical cord injury may be caused, and become apparent after delivery (Hellstrom and Sallmander, 1968; Caterini *et al.*, 1975). More recently Birnbaum (1971) described a further association, in six cases, of cervical hyperextension with Down's syndrome, and all the Down's syndrome fetuses radiographed had cervical hyperextension. A fetus with cervical hyperextension and transverse lie was illustrated by Rösslin (1513).

We have reviewed 71 Down's syndrome births occurring from 1963 to 1974 in this hospital. Of these 15 had been radiographed antenatally, and seven were shown to have an abnormal posture. Four, at bone ages 36, 39, 37 and 34 weeks, were "stargazers" (Fig. 1). The abnormal postures in the other three were: one, a face presentation (bone age 36 weeks); the second, a transverse lie (bone age 37 weeks) with a laterally flexed neck (Fig. 2); and the third, a laterally flexed body (bone age 36 weeks) with head presentation (Fig. 3).

A search was made of the radiological examinations in the period 1972–74 to look for stargazing fetuses: eight were found in 4,130 (0·19 per cent)

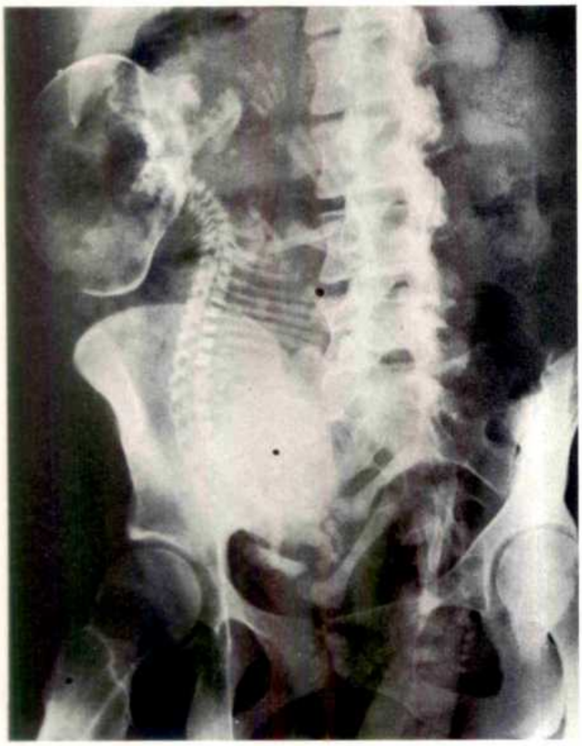

FIG. 1.

"Stargazing" fetus, which on delivery was diagnosed as a Down's syndrome.

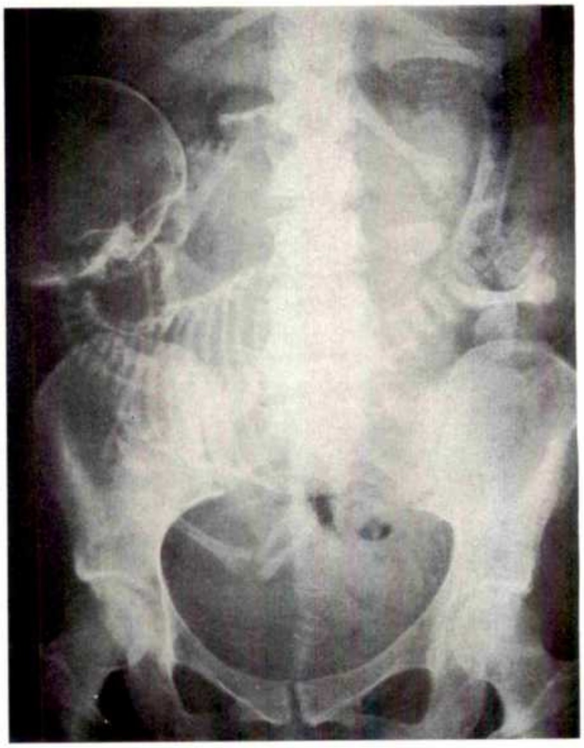

FIG. 2.

Transverse lie, with a laterally flexed neck, associated with Down's syndrome.

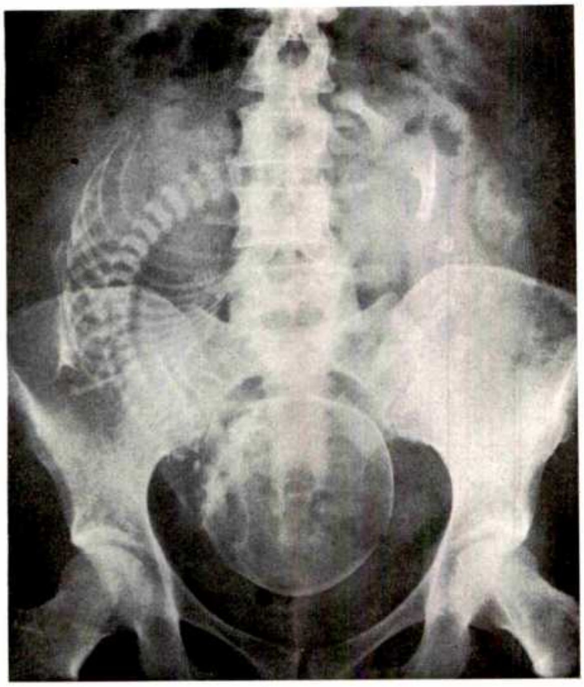

FIG. 3.
Another fetus with Down's syndrome with lateral spinal flexion.

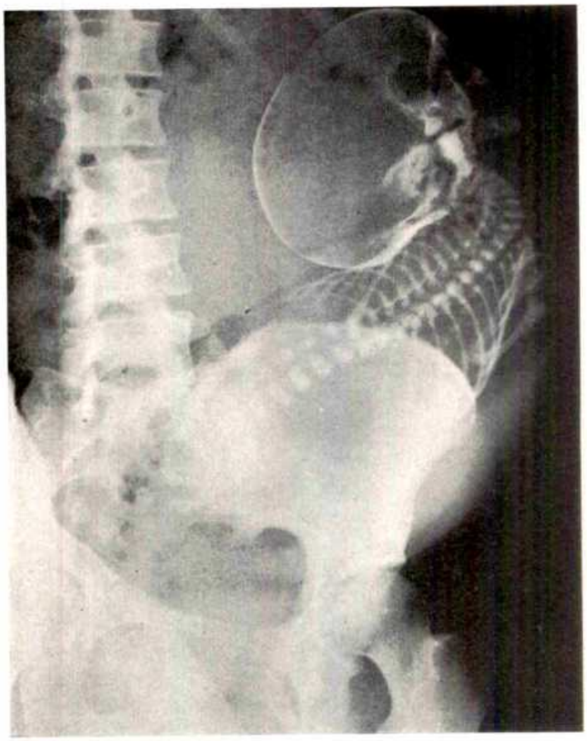

FIG. 4.
"Stargazing" fetus, with arthrogryposis (amyoplasia congenita). Note the thinness of the long bones.

examinations. Three of these were mongols, included above. Two were normal fetuses. The sixth had cervical hyperextension which persisted for three months after delivery, but who is now considered neurologically normal. The remaining two were severely hypotonic. The seventh had strikingly poor muscle bulk and tone, and no tendon reflexes were elicited. The hips were subluxed and there was bilateral talipes equinovarus. The baby fed well and is now gaining weight, being treated for its deformities, and the muscle tone is improving. The eighth infant had deformities of the hands and feet and micrognathia. The limb bones fractured easily. He died at five days, and a diagnosis of arthrogryposis (amyoplasia congenita) was made (Fig. 4). No cord injury was seen at autopsy.

DISCUSSION

In our experience nearly half the fetuses with Down's syndrome near term show an abnormal posture, and frequently they are "stargazers". Out of eight consecutive "stargazers" six were abnormal. Five showed degrees of hypotonia and one had hypertonia of the neck, persisting for three months.

Injury to the cervical cords apparent after delivery of "stargazers" has been clearly demonstrated (Behrman, 1962). It has not been definitely established whether this develops during pregnancy or during labour. Caesarian section has been advocated for "stargazers" to reduce the risk of injury (Bhagwanani *et al.*, 1973; Caterini *et al.*, 1975) although Taylor (1948) records a case of cervical cord injury after caesarian section on a "stargazing" fetus. It seems probable that in the majority of cases hypotonia allows an abnormal posture of the fetus, rather than the posture causing cord injury giving a secondary hypotonia. Both the last two cases we describe had signs indicating hypotonia of some duration—poor muscle bulk, joint subluxation or osteoporosis, and could not have had a primary injury of the cord during delivery. It remains a possibility that a hypotonic Down's syndrome baby finds itself a "stargazer" and then sustains a cervical cord injury, accentuating the hypotonia—cord injuries in the new born are difficult to diagnose clinically.

Rarely a large neck tumour will cause cervical hyperextension in a fetus. We have seen this twice, outside the period of this review. Near term the hyoid is calcified and in a neck tumour is displaced from its usual position near the mandibular angle. In both our cases the tumour showed calcification (Russell, 1973) which again allows an antenatal diagnosis. Abnormal postures of fetuses are not unusual with plural pregnancies, and the finding is probably of less significance in these circumstances. One of our Down's syndrome patients had a face presentation. There were 177 face presentations during the period of the review who had not Down's syndrome, so Down's syndrome is not likely with this finding.

Other causes of cervical hyperextension suggested by Behrman include uterine tumours and uterine malformations.

Skeletal changes in Down's syndrome are common, *e.g.* in the pelvis and fingers, but their demonstration requires careful radiographic positioning, and it is not possible to see these antenatally.

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Book review

Basic Radiation Biology. By D. J. Pizzarello and R. L. Witcofski, pp. ix + 143, 1975 (Philadelphia, Lea and Febiger, Distributed in U.K. by Henry Kimpton Publishers London), £5·90.

There are now quite a number of text-books which are intended to convey the elements of radiobiology to students, radiology residents, radiologists and radiation physicists. But to insist that there is a "best" one which makes the rest redundant is to deny the differing demands set by requirements, taste or temperament. This volume will appeal to those potential readers who are intimidated by big books containing unrelieved stretches of print, especially if it is only a basic knowledge they can hope to get from such dreary involvement. Here, we have the subject adequately covered in 18 chapters and two appendices (one on dose measurement and one on techniques for irradiating cells or animals)—all within 150 pages. Very little previous knowledge is assumed, and explanations are more patient than we might expect to find in a relatively short book. Each chapter is divided into several sequentially numbered sections, few of which extend over more than one page, and ends with a concise summary. In this way, concepts or definitions are neatly parcelled. The matter is illustrated by 40 simple figures designed more to convey the gist of a matter than to reproduce precise data.

Such an appealing presentation earns forgiveness for some few errors of fact, an occasional misconception and the odd howler; such departures have been substantially reduced from the first edition. The first reported survival curve for cells irradiated *in vivo*, although a technique is described and the correct reference given, did *not* employ ascites tumours; changing the oxygen concentration in an *in vitro* cell system does not "change *the fraction of* resistant cells"—it alters the resistance of the cells uniformly; even sixth formers will resent being told that the atmospheric pressure is 760 mm Hg and that air contains 21 per cent oxygen; and an informed layman may question: " . . . a hysterical state resembling meningitis . . . ".

We can set beside these minor irritations the exceptionally good accounts of the haematopoetic, gastrointestinal and cerebrovascular syndromes; few of the rival volumes mention that the response of the gastro-intestinal tract is affected by coincident damage to the marrow. There is a lot to be said for a study course attractively laid out in a relatively cheap book with a narrow spine

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Control of duodenal haemorrhage with cyanoacrylate

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(*Received December, 1975*)

ABSTRACT

Three cases of massive duodenal haemorrhage refractory to conventional therapy have been successfully treated by percutaneous selective intra-arterial injection of Isobutyl 2 cyanoacrylate. Case histories, injection technique and review of the literature are presented.

Embolization has been used to control gastric bleeding in patients unfit for surgery and in whom intra-arterial vasopressin infusion has failed to control haemorrhage. Experimental studies by Rosch *et al.* (1972) and Prochaska *et al.* (1973) have indicated that the gastric and duodenal arteries may be embolized with little risk of infarction by virtue of the extensive interconnection between the gastro and pancreatoduodenal plexuses. This report describes three cases of massive duodenal bleeding refractory to control by conventional means who have been successfully treated by the selective intra-arterial injection of cyanoacrylate.

CASE REPORTS

Case 1

A 53-year-old white male underwent left nephrectomy for renal carcinoma with irresectable aortic nodes. Thirteen days post-operatively brisk melaena commenced requiring the transfusion of seven units of blood during 48 hours. Laparotomy revealed an acute ulcer of the second part of the duodenum which was underrun. Vagotomy, pyloroplasty and gastrostomy were performed. Post-operatively haemoglobin stabilized at 10·8 g per cent and bleeding initially appeared to be controlled. Extensive consolidation of the left lower lobe was evident on chest X ray. Three days later haemorrhage recommenced, haemoglobin dropped to 8 g per cent and could not be maintained despite the administration of four units of blood. Gastroscopy demonstrated bleeding from the pyloroduodenal area but the exact site was not identified.

A second laparotomy and Polya gastrectomy was performed but post-operatively bleeding continued and haemoglobin fell to 7·5 g per cent. At this stage hepatic and renal decompensation were evident with bilirubin 4·7 mg per cent, AAT more than 300 mU/ml. (range 10–50), LDH more than 600 mU/ml. (range 100–225), urea 229 mg per cent (range 20–40) and the left-sided pneumonia had not improved.

Selective gastroduodenal arteriography using a No. 1 7F Cordis (Ducor) femoral visceral catheter via the right femoral artery demonstrated extravasation from the posterior superior pancreatoduodenal artery into the second part of the duodenum (Fig. 1). Infusion of pitressin (Parke Davis) 0·2 μ/minute controlled the bleeding initially but within 12 hours haemoglobin fell again to 7·5 g per cent. Repeat arteriography confirmed that the catheter was in position with its tip in the posterior superior pancreato-duodenal artery and demonstrated marked constriction of the transverse pancreatic artery and with extravasation still occurring from the same site (Fig. 2). The decrease in blood flow in the posterior superior pancreatoduodenal artery caused by the catheter and infusion of pitressin had apparently reversed flow. A second catheter placed via the left femoral artery into the superior mesenteric artery and then into the inferior pancreatoduodenal artery demonstrated that the bleeding point was fed from below as well as above. Simultaneous infusion of each catheter with pitressin 0·2 μ/minute produced radiological control of extravasation but within several hours bleeding recommenced and arteriography was repeated. Despite gross constriction of the posterior superior and inferior pancreatoduodenal arteries, extravastion was again evident. The patient by now had received over 40 units of blood and was in renal and hepatic failure with gross left-sided pneumonia. He was considered unfit for a third laparotomy and probable pancreatoduodenectomy.

Isobutyl 2 cyanoacrylate (Bucrylate Ethicon) was opacified with Hypaque powder (Winthrop) and 0·2 c.c. injected with a tuberculin syringe via a coaxial catheter (BD Formocath OD 0·38 ID 0·025) passed through the Cordis catheter into the posterior superior pancreatoduodenal artery. This completely occluded the gastroduodenal artery and glued the coaxial catheter to the vessel occluding the catheter lumen. The 7F Cordis catheter was replaced by a 7F Teflon catheter containing a fine wire snare and the fine coaxial catheter cut 15 mm from its tip. Following removal of the coaxial catheter coeliac arteriography demonstrated complete occlusion of the gastroduodenal artery with no extravasation (Fig. 3). Repeat inferior pancreatoduodenal arteriography demonstrated extravasation persisting and 0·2 c.c. of cyanoacrylate were injected to occlude this vessel. Repeat superior mesenteric arteriography indicated control of extravasation and filling of the anterior superior pancreatoduodenal artery via collaterals (Fig. 4).

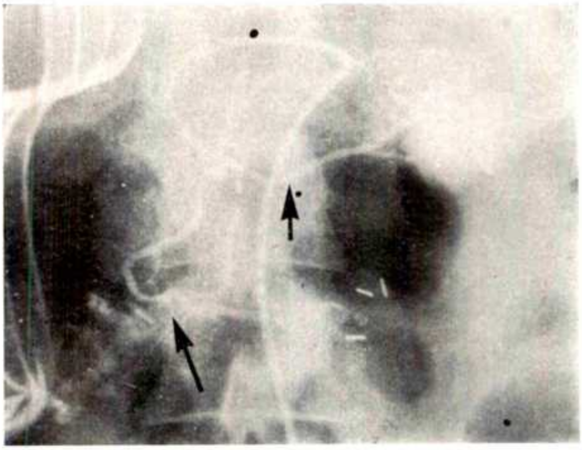

FIG. 1.

Selective posterior superior pancreatoduodenal arteriogram. Extravasation into second part of duodenum (long arrow). Transverse pancreatic artery (short arrow).

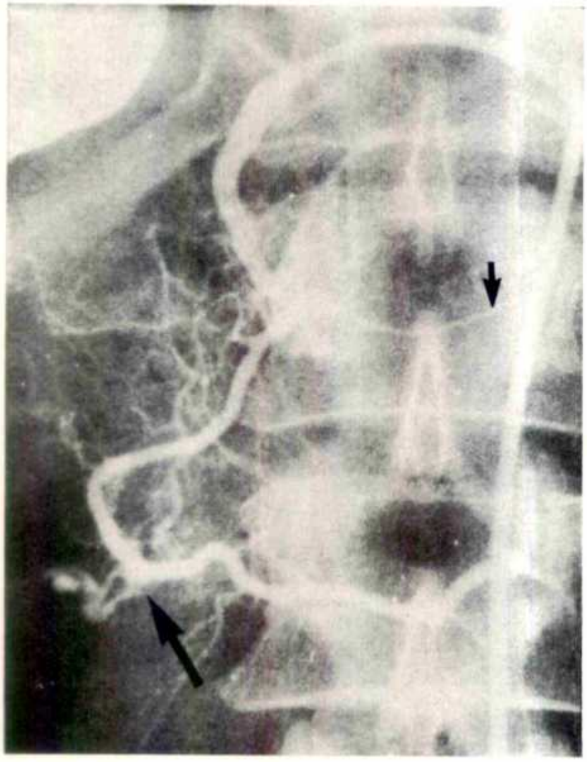

Fig. 2.

Repeat arteriography after 24-hour perfusion with vasopressin. Poor posterior superior pancreatoduodenal constriction and persistent extravasation (long arrow). Constricted transverse pancreatic artery (short arrow).

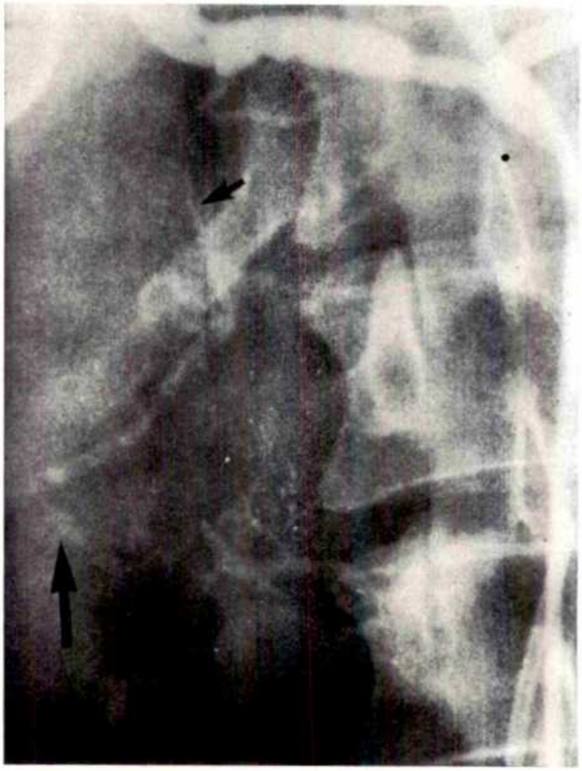

Fig. 3.

Post-cyanoacrylate coeliac arteriogram with occlusion of the gastroduodenal artery and faintly opacified vascular loop (long arrow). Short fragment of coaxial catheter glued into proximal posterior superior pancreatoduodenal artery (short arrow). Cyanoacrylate opacified with Hypaque powder.

Following the injection of cyanoacrylate haemorrhage ceased dramatically with stabilization of haemoglobin at 10 g per cent and clearing of the gastric aspirate. Moderate epigastric pain developed within 30 minutes of injection and persisted for 24 hours. No further bleeding occurred thereafter and following a protracted convalescence the patient was discharged. During a nine-month follow-up period there have been no further episodes of gastro-intestinal bleeding. Attempts to evaluate the afferent loop by barium studies have been unsuccessful.

Case 2

A white 70-year-old female with long-standing hypertension underwent an anterior resection for carcinoma of the rectosigmoid. On the twelfth post-operative day melaena and aspiration of old blood from the nasogastric tube commenced and haemoglobin fell to 9 g per cent. Following transfusion the patient's condition stabilized but several days later she passed a massive amount of melaena and became shocked with a blood pressure of 95/50 mmHg and haemoglobin of 4 g per cent. Gastroscopy revealed an acute duodenal ulcer. Despite the administration of a total of 12 units of blood the haemoglobin level could not be maintained. The patient refused the option of surgery and was consequently referred for angiography and conservative control of the bleeding.

Selective gastroduodenal arteriography using a 7F Cordis femoral visceral No. 1 catheter demonstrated brisk extravasation of contrast into the first part of the duodenum (Fig. 5). Pitressin in a dose of $0{\cdot}2\ \mu$/minute was infused and radiographic control of the bleeding was apparent. During the ensuing 12 hours however bleeding continued despite the infusion. Repeat arteriography confirmed satisfactory catheter placement in the presence of marked constriction of the gastroduodenal artery but persistent extravasation of contrast. In view of the patient's age and adamant refusal of surgery in the face of inadequate control by pitressin infusion, gastroduodenal artery injection of cyanoacrylate was carried out. A total volume of 0·2 c.c. was injected in divided doses of 0·1 c.c. without complication by "sandwiching" the cyanoacrylate between saline. This partially occluded the gastroduodenal artery and immediately halted the extravasation of contrast from the bleeding site (Fig. 6). Clinical evidence of control of the haemorrhage was soon evident with clearing of the nasogastric aspirate and stabilization of blood pressure and haemoglobin. Apart from mild epigastric discomfort for 12 hours there were no other abdominal symptoms and no further bleeding from the gastro-intestinal tract occurred. Follow-up over a four-month period has been uneventful.

Case 3

A black female of 42 years presented to a country hospital with a one-month history of epigastric pain, radiating to the back, weight loss and intermittent melaena stools. On

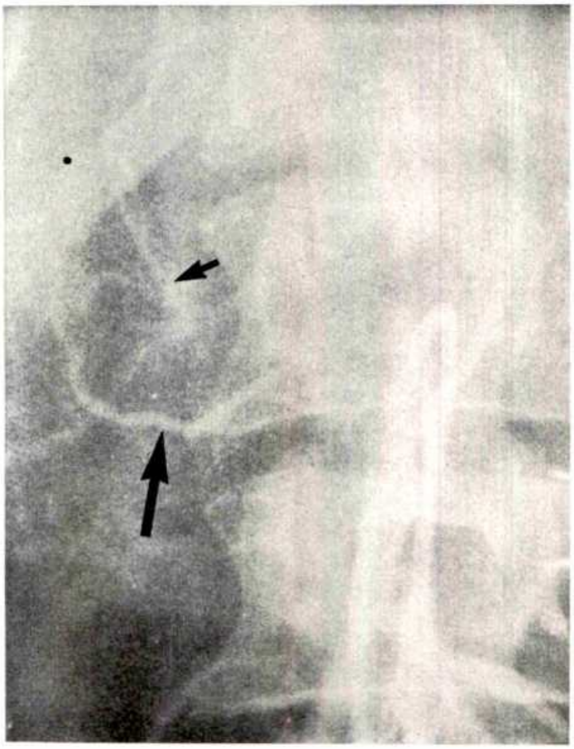

FIG. 4.

Post-cyanoacrylate superior mesenteric arteriogram. Occlusion of the inferior pancreatoduodenal artery with filling of the anterior superior pancreatoduodenal artery (long arrow). Tip of coaxial catheter before removal (short arrow).

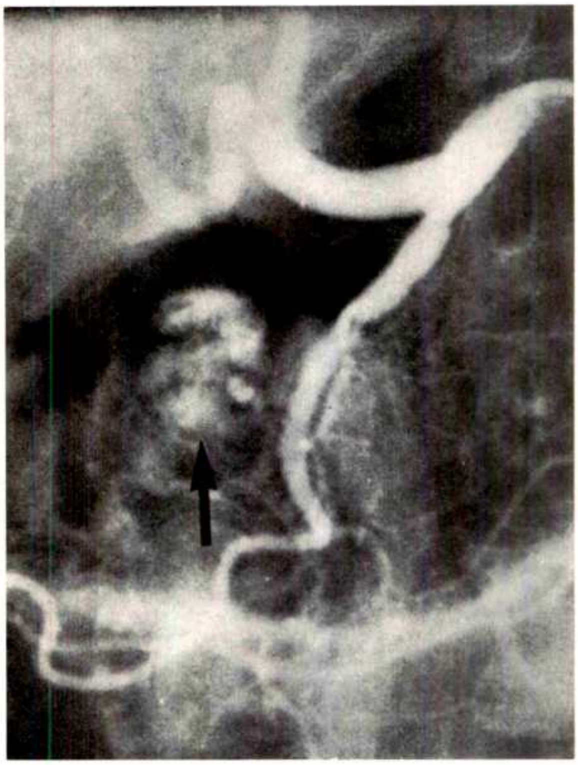

FIG. 5.

Gastroduodenal arteriogram. Extravasation into first part of duodenum (long arrow).

clinical examination she was pale and a firm 7 × 5 cm epigastric mass was palpable with an audible bruit over it. The stool was positive for occult blood and haemoglobin on admission 8·8 g per cent. She was initially transfused to a haemoglobin of 12 g per cent but shortly thereafter developed brisk haematemesis requiring further blood replacement as her haemoglobin dropped to 7·4 g per cent. X-ray chest and abdomen were normal and barium meal demonstrated deformity of the duodenal cap.

Laparotomy revealed a 9 cm mass in the region of the duodenal loop with the head and neck of the pancreas stretched and densely adherent to the antero-inferior aspect. The mass was pulsatile and exploration of the lesser sac demonstrated the hepatic artery leaving its superior aspect and the splenic artery leaving the left lateral side. The lesion was thought to be a coeliac artery aneurysm but attempts to gain proximal control were unsuccessful and the laparotomy was closed. Her post-operative course until the eighth day was uneventful when massive haematemesis again commenced and in the ensuing 48 hours six units of blood were administered.

Arteriography demonstrated a pear-shaped 6 × 4 cm aneurysm arising from the gastroduodenal artery (Fig. 7). Cyanoacrylate was not immediately available and in an attempt to cause thrombosis of the aneurysm, injection with chopped Gelfoam sponge (Upjohn) via the 7F Cordis catheter was carried out. Clotting time was in excess of 30 minutes and the gelfoam merely circulated in the aneurysm without causing thrombosis. The slight diastolic recoil of the aneurysm caused reflux of gelfoam fragments past the catheter tip in the gastroduodenal artery with resultant embolization of the branches of the right hepatic artery (Fig. 8). Cyanoacrylate was injected in divided doses of 0·2 c.c. as in Case 2 producing complete occlusion of the gastroduodenal and right hepatic arteries with cessation of extravasation from the aneurysm (Fig. 9).

Following the procedure the patient experienced a moderate degree of epigastric pain which lasted several hours, the nasogastric aspirate cleared rapidly, blood pressure and haemoglobin stabilized and there was no further bleeding. Her post-operative course thereafter was uneventful although transient elevation of hepatic enzymes occurred. During a three-month follow-up period the patient has remained well. Repeat arteriography demonstrated proximal extension of the hepatic occlusion with no evidence of aneurysmal filling (Fig. 10).

DISCUSSION

Isobutyl 2 cyanoacrylate is a monomer of low viscosity which polymerizes immediately on contact with blood and the vessel wall to form a spongy mass that will produce permanent occlusion of the lumen (Matsumoto 1972; Zanetti and Sherman,

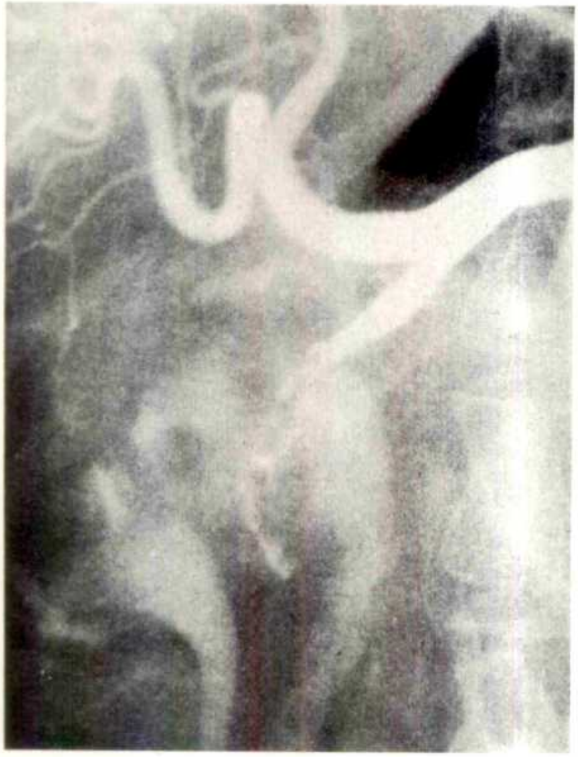

FIG. 6.
Post-cyanoacrylate occlusion of the gastroduodenal artery.

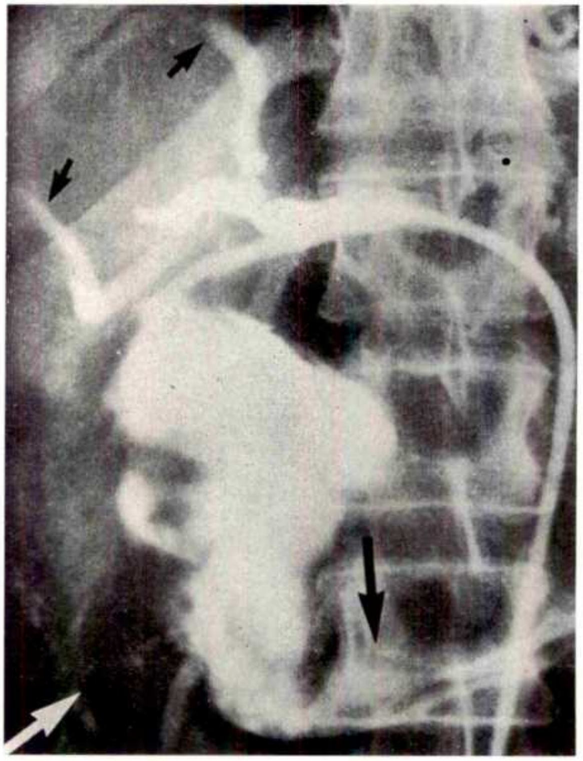

FIG. 8.
Gastroduodenal artery aneurysm six hours post Gelfoam injection. Partial occlusion of the aneurysm lumen. Extravasation into stomach and duodenum (long arrows). Gelfoam embolization of right hepatic artery branches (short arrows).

1972). Distal embolization will occur if it is injected slowly into a rapidly flowing bloodstream but proximal occlusion will be produced if blood flow is slowed and the bolus of cyanoacrylate is injected more rapidly (Kerber, 1975).

Control of the injection may be facilitated by opacification. Tantalum powder (Rosch *et al.*, 1975) has been used for this purpose and in Case 1 this was attempted with Hypaque powder (Winthrop) which yielded a poor degree of radiographic density and did not aid the control of injection.

Cyanoacrylate appears to elicit minimal tissue reaction (Zanetti and Sherman, 1972). Experimentally the material has been used to occlude gastric and duodenal vessels, obliterate aneurysms, A.V.

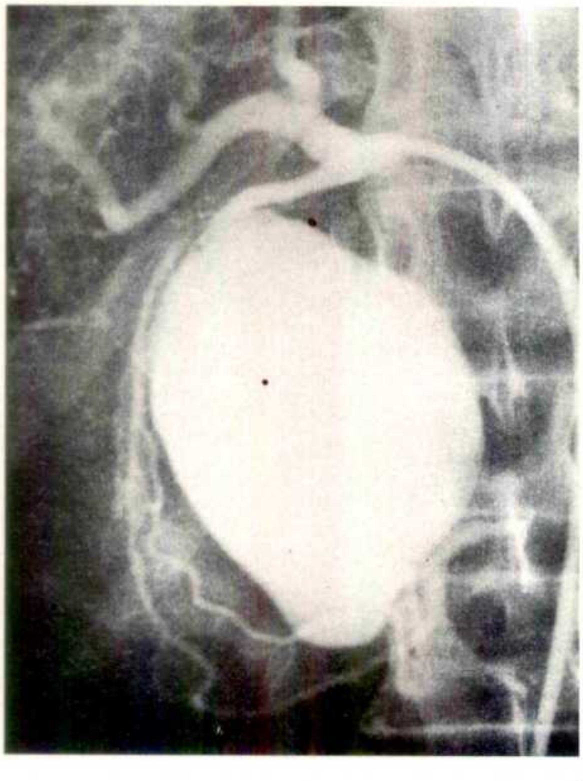

FIG. 7.
Gastroduodenal artery aneurysm pre-Gelfoam injection.

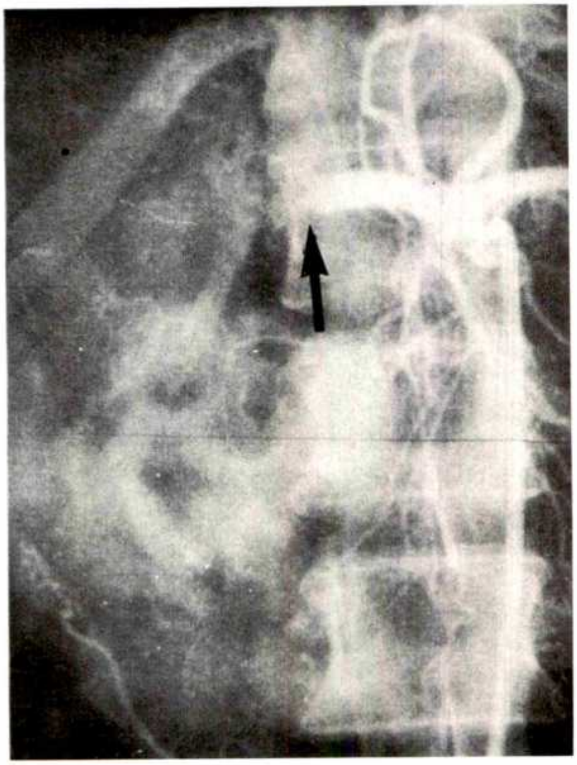

FIG. 9.
Post cyanoacrylate occlusion of right hepatic artery (long arrow).

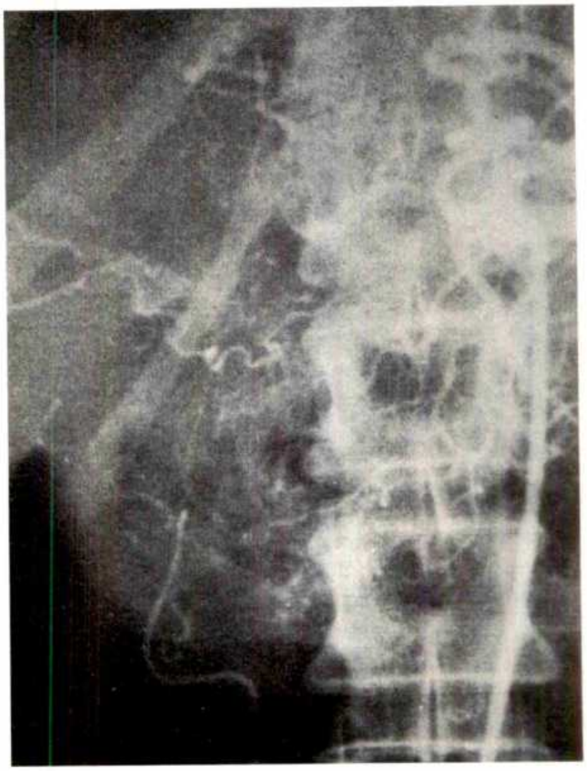

FIG. 10.
Three months post-cyanoacrylate. Hepatic artery occlusion has propagated proximally.

fistulae and the gastric coronary vein (Zanetti and Sherman, 1972; Kerber, 1975; Rosch *et al.*, 1975). Clinically it has been used in the management of cerebrospinal rhinorrhoea and to achieve haemostasis (Lehman *et al.*, 1967; Van der Ark *et al.*, 1970; Matsumoto *et al.*, 1969). Renal ablation in lieu of nephrectomy and hypogastric artery occlusion for pelvic haemorrhage have also been carried out with this material (Dotter *et al.*, 1975).

The problems encountered with its use in Case 1 were the adhesion of the catheter to the vessel wall and occlusion of the catheter lumen. This occurred because too large a volume was injected too rapidly and the catheter was not withdrawn simultaneously. The subsequent two cases were managed by serial injections of small volumes of 0·1 c.c. "sandwiched" between saline. This method avoided the problems encountered in Case 1 and kept the catheter patent for post-cyanoacrylate arteriography in order to evaluate the degree of occlusion obtained. The rate of delivery using this method was 0·1 c.c. in less than one second. Coaxial catheter manipulation was not required and there was also no need to withdraw the catheter during the injection to avoid adhesion to the vessel wall. Blood flow in the injected vessels in all three cases was grossly reduced at the time of injection, in Cases 1 and 2 by the catheter tip lodged in a small vessel following pitressin infusion and in Case 3 by the aneurysmal nature of the lesion and the previous injection of Gelfoam. The occlusions produced in these cases were sufficiently proximal to prevent infarction which has occurred with autologous clot as a left gastric embolic agent in man (Prochaska *et al.*, 1973) and with cyanoacrylate injected slowly in larger doses as a duodenal embolic agent in dogs (Dotter *et al.*, 1975).

Although permanence of occlusion in Case 1 and 2 was probably not essential for a favourable clinical outcome it was certainly an important consideration in Case 3 and the follow-up coeliac axis arteriogram at three months clearly showed no evidence of recanalization.

In all three patients the injection of cyanoacrylate was carried out with informed consent as a treatment of last resort, when conventional methods of management had failed and a fatal outcome appeared to be inevitable. The favourable results in these three cases and the experimental work currently being carried out with cynaoacrylate indicate that it may have great potential as a tool in the future of intervention radiology.

ACKNOWLEDGMENT

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Book review

Cancer of the lung. By H. G. Seydel, A. Chait and J. T. Gmelich, p.200, 1975 (Chichester, Sussex, John Wiley and Sons), £14·00.

It is a pleasure to see the recent interest in this depressing malignancy; instead of being ignored because the prognosis is poor we are now appreciating more publications dealing with the oncological approach. The number of patients who are cured is disappointingly small, and although admittedly some advances have been made in therapeutic procedures, these have probably reached the maximum. But, improvements can still be made in the management of these patients, by selecting suitable patients for radical treatment, by rationalizing the use of combined methods of treatment and by developing more suitable chemotherapeutic agents. It is essential that no chance of a cure is lost, that operable patients are referred for surgery, that those suitable for radical radiotherapy receive it and that where there is evidence of any improvement in survival by the use of combination therapy this is used. Other forms of therapy should be reserved for the less favourable patients and for palliation. However, until we can find definite methods of improving the existing survival rates our attack must be based on early diagnosis and prevention.

This book sets out to present the facts about cancer of the lung, to foster a better understanding of this disease and to stimulate an interest in such aspects as prevention, diagnosis and treatment. The chapters are concise and pertinent and adequate references are given for those who wish to read further. The chapter on pathology, written entirely by one of the authors, is of particular merit. Another comprehensive chapter on diagnostic radiology, also written by one author and profusely illustrated, gives a clear account of the radiological and isotope uptake studies. Surgery and both curative and palliative radiotherapy are adequately covered, but some workers would perhaps suggest that the chapter on chemotherapy could be extended.

The text is lively and very readable, there are many illustrations and the whole book is beautifully produced. I enjoyed reading it. It will certainly have a place in the medical library; it should be a boon to trainees and of interest to all those concerned with the management of the patient with cancer of the lung.

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Selective renal occlusion phlebography with a balloon catheter

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ABSTRACT

Technique of selective renal occlusion phlebography is described. For the temporary occlusion of the renal vein a Swan-Ganz or Dotter-Lucas balloon catheter are used. The balloon catheter is directed into the renal vein using a Desilets-Hoffman or EDSLAB introducer. Occlusion of the renal vein is achieved by insufflation of 2–3 ml. air into the balloon of the catheter. Selective renal occlusion phlebography leads to optimal retrograde opacification of the renal venous system.

Various methods of renal phlebography have been advocated, because renal veins are usually poorly opacified by injection of the contrast agent against the copious flow of renal venous blood (Table I). These methods include selective retrograde renal vein catheterization, percutaneous transrenal phlebography, injection of contrast medium into the left spermatic vein, occlusion or vasoconstriction of the renal artery to diminish renal arterial inflow and blockade of the renal vein or occlusion of the inferior vena cava proximal and distal to the renal venous orifices—using one or two balloon techniques—in order to increase the reflux of contrast medium into the renal veins. Some of these techniques are relatively successful, others are cumbersome and unreliable.

In a search for simple and practical methods for the radiographic demonstration of renal veins the method of selective occlusion phlebography using a balloon catheter was developed. This report concerns technical aspects as well as indications, contraindications and limitations of selective renal occlusion phlebography.

TECHNIQUE OF RENAL OCCLUSION PHLEBOGRAPHY

Preparation of the patient

In anxious patients premedication consists of the intramuscular injection of 10 mg Diazepam (Valium) 30 minutes prior to the examination.

Catheters and renal vein catheterization

The end-hole Swan-Ganz balloon catheter size 7F or Dotter-Lucas balloon catheter size 8·5 F are used. The balloon catheter is introduced into the renal vein by the femoral or cubital route. For the introduction of the balloon catheter a Desilets-Hoffman or EDSLAB introducer are suitable. Under fluoroscopic guidance the balloon catheter is directed into the right or the left renal vein. Following successful catheterization of a renal vein, occlusion is achieved by insufflation of 2–3 ml. air into the balloon of the catheter. The position of the catheter and complete occlusion of the renal vein are controlled fluoroscopically by means of manual injection of 2–3 ml. of contrast medium.

TABLE I

REVIEW OF METHODS OF RENAL PHLEBOGRAPHY

Method	Experimental phlebography	Clinical phlebography
Retrograde selective phleobraphy		Dalla Palma and Servello, 1956 Harrison *et al.*, 1956 Steiner, 1957 Peart and Sutton, 1958
Percutaneous transrenal phlebography	Beres *et al.*, 1964 Gilsanz *et al.*, 1965	Léger *et al.*, 1957 Beres *et al.*, 1964 Gilsanz *et al.*, 1965
Phlebography via vena spermatica		Gospodinow and Topalow, 1955 Peluffo and Paez, 1963
Phlebography by: occlusion of renal artery; occlusion of renal vein; occlusion of inferior vena cava	Dalla Palma and Pistolesi, 1954 Gillot and Hureau, 1961 Thalheimer and Gilot, 1962 Haverling, 1966 Takaro and Kivirand, 1966	Haverling, 1969 Georgi *et al.*, 1975 Takaro *et al.*, 1970 Dalla Palma and Servello, 1954 Gillot *et al.*, 1965
Pharmaco-phlebography	Takaro and Kivirand, 1966	Olin and Reuter, 1965 Gyepes *et al.*, 1969 Than and Ténye, 1970 Takaro *et al.*, 1970 Braedel *et al.*, 1974

Contrast medium and technique of injection

For the opacification of the renal veins 15–25 ml. of a 66 per cent contrast medium (Telebrix 300) at a flow rate of 5–10 ml./second are injected, using an automatic injector (Contrac). Films are taken at one second intervals over a 12-second period. The filming is started after 10–15 ml. of contrast material have been injected.

INDICATIONS

Renal phlebography is indicated:

(1) in suspected renal vein thrombosis (Harrison *et al.*, 1956; Steiner, 1957, 1960; Bücheler *et al.*, 1967; Chait *et al.*, 1968; Gyepes *et al.*, 1969).

(2) in cases with recent pulmonary infarction, in which the source of the embolus is clinically not obvious (Steiner, 1960).

(3) for delineation of poorly vascularized neoplasms and metastases of the kidney (Smith *et al.*, 1975).

(4) for the determination of venous involvement of renal and retroperitoneal tumours (Fig. 1) (Harrison *et al.*, 1956; Fuchs, 1961; March and Halpern, 1963; Kahn, 1969).

(5) in evaluation of a non-functioning kidney (Takaro *et al.*, 1970).

(6) for the differentiation between congenitally absent and small contracted kidney (Athanasoulis *et al.*, 1973).

(7) for demonstrating vascular involvement in cases of renal trauma (Harrison *et al.*, 1956) (this is of special interest in cases in which arterial catheterization is not possible).

(8) for demonstrating the patency of splenorenal shunts (Caron *et al.*, 1963).

(9) for sampling of renal venous blood for renin determination, because the knowledge of the number and location of renal veins and existence of an anomalous venous drainage may be of significance (Fig. 2) (Kahn, 1969; Takaro *et al.*, 1970).

CONTRAINDICATIONS AND LIMITATIONS

Before selective renal vein catheterization in patients with suspected renal vein thrombosis is tried, cavography should be performed to exclude thrombosis of the inferior vena cava. There is a

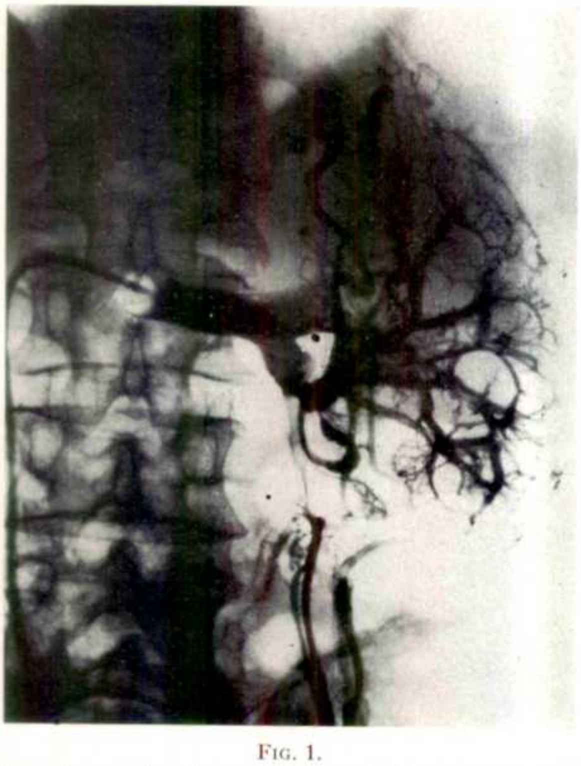

FIG. 1.

Selective renal occlusion phlebography in a patient with a retroperitoneal mass. Irregular renal veins due to tumour involvement in the caudal portion of the left kidney. Demonstration of regular venous patterns including small cortical veins in the cranial half of the kidney.

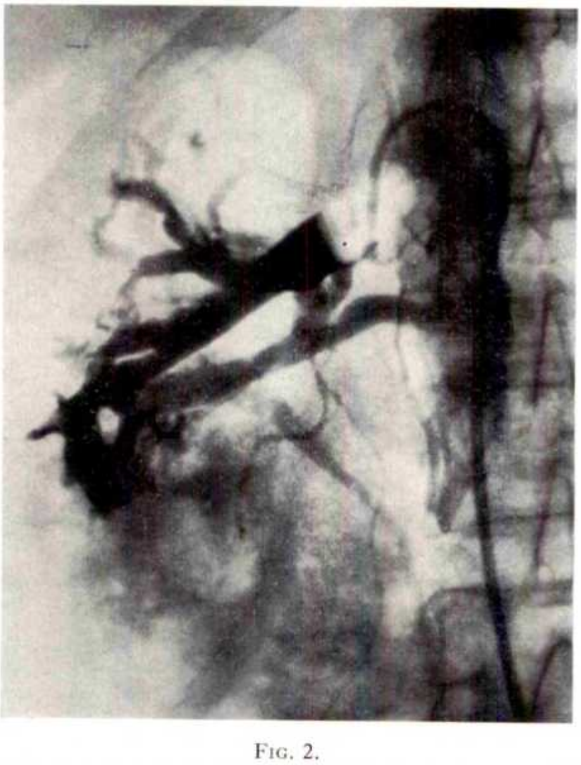

FIG. 2.

Selective renal occlusion phlebography with occlusion of the upper right renal vein with a balloon catheter. Contrast agent flow via caudal renal vein with opacification of inferior vena cava.

theoretical danger of dislodging clot or tumour material from the renal vein, causing a pulmonary embolus. Therefore catheterization should be performed very cautiously.

CONCLUSIONS

In spite of clinical interest and of the high diagnostic value of the procedure, renal phlebography was relatively rarely performed, because of technical difficulties of current methods.

Selective renal occlusion phlebography is a simple and safe technique, based on the temporary occlusion of the renal vein by a balloon. Occlusion of the venous blood flow leads to optimal retrograde opacification of the entire renal venous system.

It is believed that the simplification of the technique may lead to wider use of this procedure in the study of renal diseases and better appreciation of the complexities of the renal venous system.

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Radiological manifestations of oesophageal involvement in acanthosis nigricans

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ABSTRACT

Radiologic features of two cases of acanthosis nigricans with oesophageal involvement are reported.

The first case demonstrated diffuse, granular shadows throughout the oesophagus which were difficult to differentiate from oesophageal moniliasis. Another case showed many discrete and tiny elevations resembling pseudopolyposis of the colon.

Emphasis is placed on radiological differential diagnosis from moniliasis and leukoplakia of the oesophagus.

Acanthosis nigricans is a disease characterized by the triad of papillomatous hyperplasia, pigmentation and hyperkeratosis of the skin. Involvement of the mucous membranes is not unusual. A "malignant" type is well known due to its association with visceral malignant disease.

Two cases of malignant acanthosis nigricans with oesophageal involvement were radiologically examined.

CASE REPORTS

Case 1

A Japanese male patient aged 67 years with a history of gastric cancer resected two years previously was examined because of epigastric pain and slight dysphagia. He had histologically proven generalized acanthosis nigricans with oral involvement.

Passage of barium through the oesophagus was moderately delayed but peristalsis was well preserved. Many granular shadows densely distributed throughout the oesophagus were shown in the double contrast film (Fig. 1). They were innumerable in number, elliptical in shape and up to several millimetres in diameter.

Endoscopic examination revealed a thickened and finely granular oesophageal mucosa with several larger elevations up to 1 cm in diameter. The rest of the alimentary tract was essentially normal radiologically and endoscopically except for cancerous erosion at the gastro-duodenal stoma.

Case 2

A Japanese man aged 58 years with histologically proven acanthosis nigricans of the skin and oral mucosa was referred for investigation.

Barium meal revealed a malignant ulcer at the mid-oesophagus which was diagnosed as a squamous cell carcinoma by biopsy. On a double contrast study, numerous tiny, discrete translucencies which were easily distinguished from air bubbles were also demonstrated (Fig. 2). Some were round and others were elliptical or bar-shaped. The majority had sharp margins. The oesophageal wall was smooth with scattered small defects without spiculation.

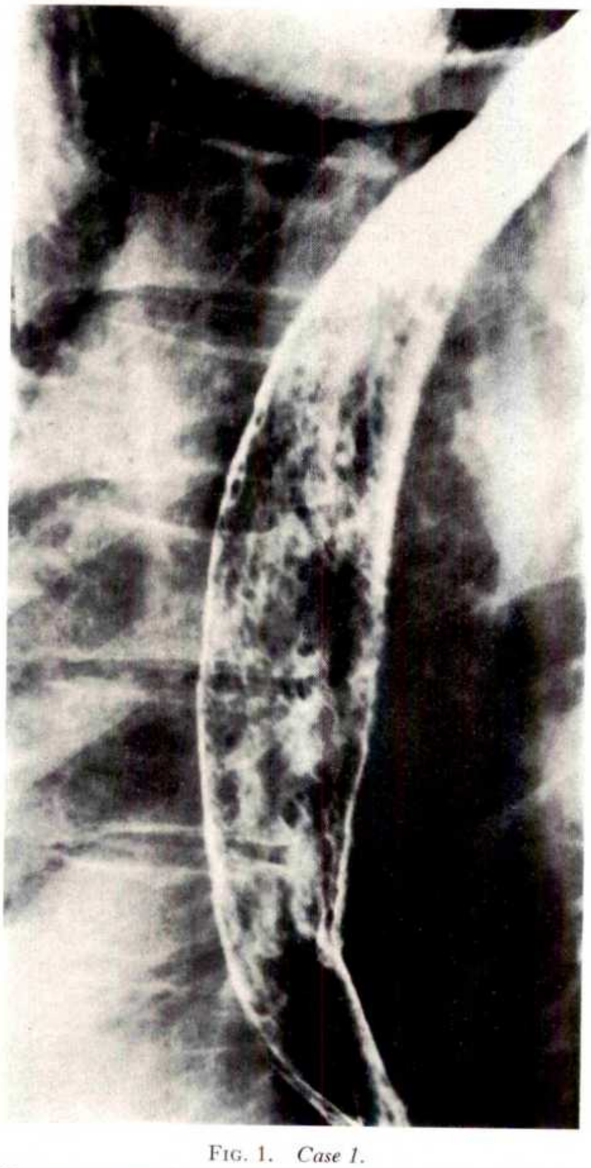

FIG. 1. *Case 1.*
Numerous granular shadows throughout the oesophagus.

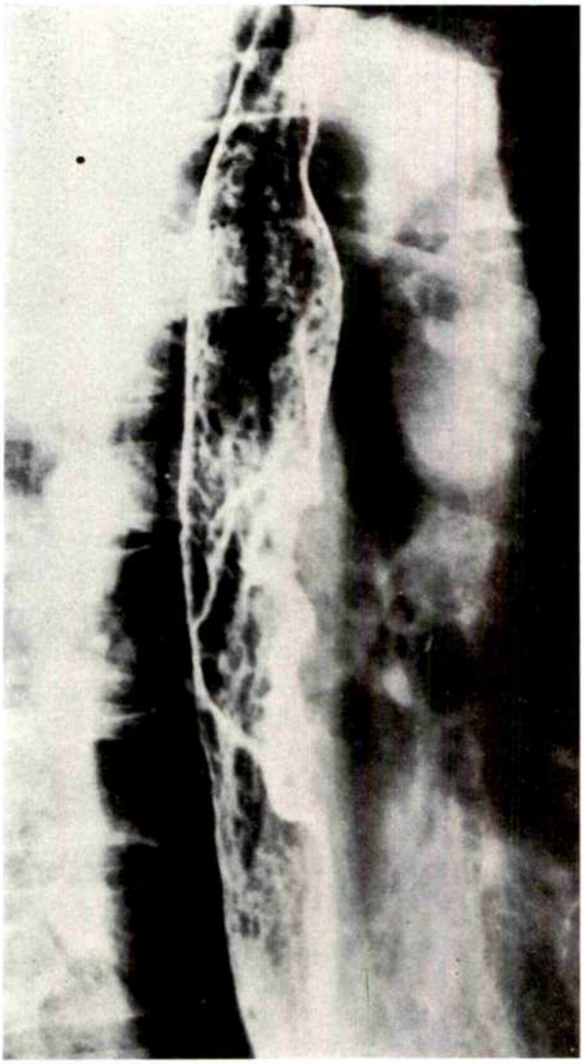

FIG. 2. *Case 2.*
Many tiny but discrete protrusions throughout over all the gullet.

Movement and width of the oesophagus were within normal limits except in the mid-oesophagus involved by cancer.

Papillomatous elevations as well as leukoplakia were recognized endoscopically.

COMMENT

Involvement of the oesophagus in acanthosis nigricans has been well known among pathologists. However, only a few clinical reports have been published. Pasini first reported endoscopic observations in 1950. There are no English papers on the radiological findings of oesophageal acanthosis nigricans as far as the authors can ascertain. Both our two cases revealed radiographically diffuse, granular shadows which should be differentiated from moniliasis and leukoplakia of the oesophagus.

Oesophageal moniliasis frequently shows the following radiological signs: nodular filling defects (granular shadows in the double contrast study), shaggy outline, involvement of the lower two-thirds, and diminished oesophageal peristalsis. All the above were shown in the first case in various degrees.

However, the following features favour the diagnosis of acanthosis nigricans; slight disturbance of peristalsis and uneveness of oesophageal contour caused by multiple small filling defects, not by spiculated ulceration. These findings reflect the superficial nature of the disease.

Leukoplakia of the oesophagus is epithelial hyperplasia, round in shape, small in size and often multiple. On occasions it is recognized radiologically as numbers of small protrusions with hazy boundaries (Endo *et al.*, 1973). In contrast, Case 2 had multiple well-defined elevations and revealed shadows similar to pseudopolyposis in the colon. This sharpness of the boundary and association of acanthosis in the oral mucosa appear to serve as differential points between the two diseases.

Progressive systemic sclerosis, peptic oesophagitis, corrosive oesophagitis, oesophageal varices and oesophagitis cystica occasionally show diffuse granular shadows of various size and range in the oesophagus.

Finally, we would like to emphasize the value of double contrast studies in the oesophagus to demonstrate detail (Shirakabe *et al.*, 1973).

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Pineal gland calcification (PGC) in Ugandans. A radiological study of 200 isolated pineal glands

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Abstract

Two hundred formalin-fixed pineal glands from consecutive unselected post-mortems on Ugandan Africans have been X-rayed. The degree of pineal gland calcification has been divided into four stages and it is shown that 43 per cent of all pineal glands after the age of ten years are likely to be detected in an ordinary skull X ray. This high percentage of calcification contrasts with the previously reported low figure from races other than whites. The pineal glands from females were more often calcified and heavier than those from males; however, the stalks of pineal glands from males were calcified more frequently than those of females. The average weight per decade was almost constant. In Ugandan Africans the pineal glands were significantly lighter than in Caucasians, and a possible reason for this is briefly discussed.

Pineal gland calcification (PGC) in man was discovered in necropsies over 300 years ago (Scharenberger and Liss, 1965). Schüller (1918) was the first to describe PGC on a plain skull radiograph. Since then the calcified pineal gland has served as a mark of brain topography, and any shift is an aid in localizing intracranial pathology. Kitay and Altschule (1954) in their review listed the incidence of PGC between 33–76 per cent in a Caucasian population. These figures contrast with reports from other races where the incidence of PGC has been reported to be low (between 5 and 24 per cent) (Chiba and Yamada, 1948; Pillai, 1968; Daramola and Olowu, 1972; McKay, 1973; Adeloye and Felson, 1974). No detailed figures were available from East Africa; however, the impression was that PGC was an uncommon finding (Murphy, 1968). The purpose of this paper is to report on the radiological incidence of calcification in isolated pineal glands in Ugandan Black Africans.

Material and Methods

Pineal glands were collected from 230 consecutive routine post-mortems performed in the Department of Pathology, Makerere University Kampala. No selection for chronic and acute illness or malignancy was made.

The pineals were removed from the brain, and initially they were resected as near as possible to the 3rd ventricle. However, early during the study, stalk calcification was observed macroscopically, and from then onwards a more generous resection of the pineal gland area was performed, including the thalamus and postero-superior portions of the 3rd ventricle. The glands were immediately fixed in 10 per cent formalin for at least two days. They were then dissected by stripping off the meninges and removing the surrounding brain tissue but leaving the stalk with its superior and inferior laminae attached to the pineal gland.

The pineal glands were then X-rayed using a Watson 50 kV 50 mA laboratory X-ray machine. The tube distance was 64 cm, exposure time 30 seconds at 30 kV and 20 mA. Fine grain film (Microtex, Kodak) was used and developed in undiluted Developer D76. The films were examined for calcification and divided into four categories according to the amount of opacity detected (Fig. 1):

Degree 0: No calcification seen on radiograph.

Degree I: Minimal calcification, thought to be not detectable in an ordinary skull radiograph.

Degree II: Moderate calcification, thought to be most likely detectable in an ordinary skull radiograph.

Degree III: Marked calcification, thought to be easily detectable in an ordinary skull radiograph.

The stalk was removed from the pineal gland and the organ was blotted dry with filter-paper. The weight of the pineal gland was then determined to the nearest milligram using an electric balance (Mettler Type H3). The weight was transformed to the cube root, for convenient comparison with previous studies (Rodin and Overall, 1967; Tapp and Blumfield, 1970; Tapp and Huxley, 1971).

To evaluate the degree of calcification that would be apparent in a clinical radiograph of a skull, examples of the four degrees of calcification indicated by pins were placed on an X-ray film cassette with the authors skull superimposed, and clinical radiographs taken (Tube distance 1 m, 85 kV, 72 mA, 0·21 seconds). It is interesting to note that the routine exposure (1 m, 78 kV, 75 mA, 0·21 seconds)

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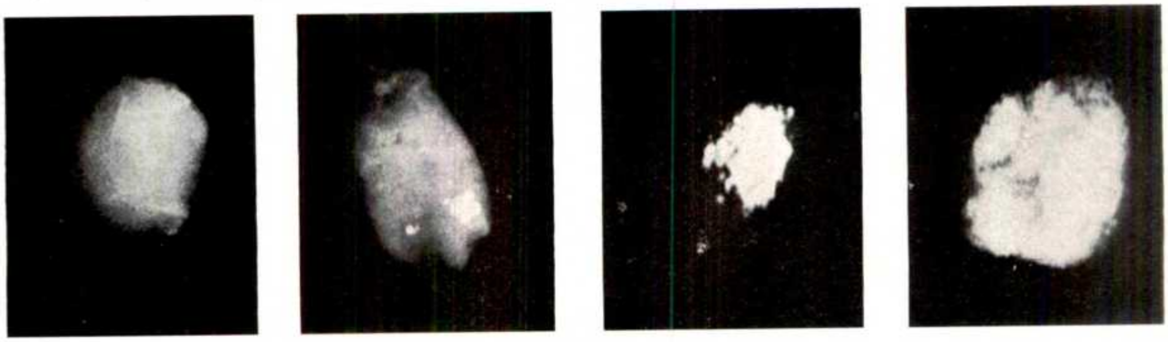


FIG. 1.

Degree of calcification as used for classification (from left to right).

Degree 0	No calcification.
Degree I	Minimal calcification.
Degree II	Moderate calcification.
Degree III	Marked calcification.

was not sufficient to visualize the staged calcified pineal glands on a superimposed skull.

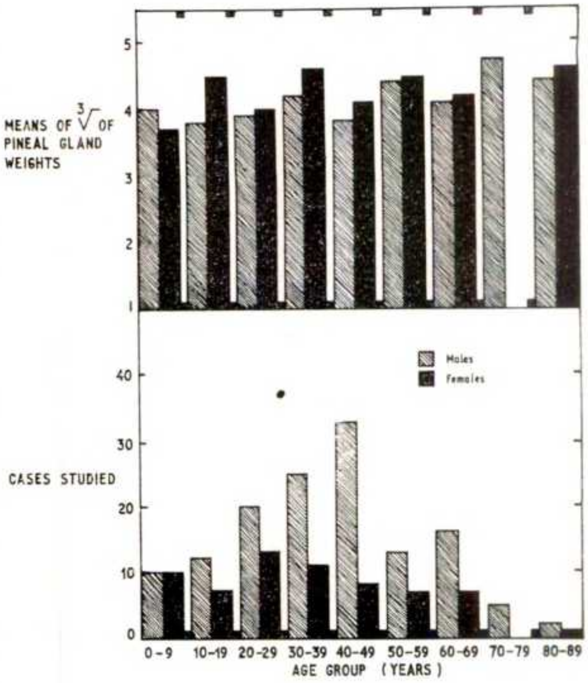
RESULTS

Two hundred pineal glands were accepted for final analysis and the age and sex distribution is given in Table I. There is a usual male predominance in the post-mortems and as the study was a consecutive one, no attempt was made to correct this proportion which stands at 2·1:1 for males (136:64). The tribes were grouped into geographical regions: 86 were from the south, 33 from the west, 16 from the north and ten from the east of Uganda, 31 were from Rwanda Burundi, seven were from other African territories, no tribe was given in 17 cases.

The weight of the pineals was expressed as a cube root of its weight in milligrams. The mean cube root per decade and sex is given in Table I, showing that it varied between 3·7 and 4·7. The mean pineal weight in females was higher than in males, apart from those in the first decade. The average cube root for all ages was higher in females than in males and stands at 4·2 to 4·1. Table II shows the presence or absence of calcification in 200 pineal glands correlated to age and sex. There were 125 calcified pineal glands, 75 showed no radiologically detectable calcification. In the first decade no calcification was observed in either sex, this group was consequently excluded from the following comparative figures. The calcification gradually increased subsequently. The sex ratio of the calcified pineals was 1·9:1 for males (83:42) whereas in non-calcified pineals, it was 3·5:1 (43:12). There was therefore a significant excess of non-calcified pineal glands in males compared to females or in other words the pineal glands of females were more often calcified.

TABLE I

Sex and age distribution of 200 cases in which pineal glands were analysed. The upper histogram shows the average weight in milligrams expressed in cube roots for the same groups.



The site of PGC varied. Figure 2 shows that calcification can occur either in the pineal gland or in the stalk or in both. Of the 110 stalks examined, 65 (=59 per cent) showed calcifications of which 12 had stalk calcification alone. Thus 53 had both stalk and pineal gland calcification. The sex ratio of these 110 was 2·6:1 (80:30) for the males. The sex ratio for those with stalk calcification was 3·6:1 (51:14) and for those without 1·8:1 (29:16) for the males. Therefore males showed stalk calcification more often than females.

Table III shows the degree of PGC in relation to sex and age decades. From this it is evident that the maximal calcification is not reached in both sexes in the second decade, however, it is present from the third decade, exception made for the fourth decade in males and the sixth decade for females both of which show a total absence of Degree III.

TABLE II

The 200 pineal glands grouped according to sex and age with relation to presence or absence of calcification.

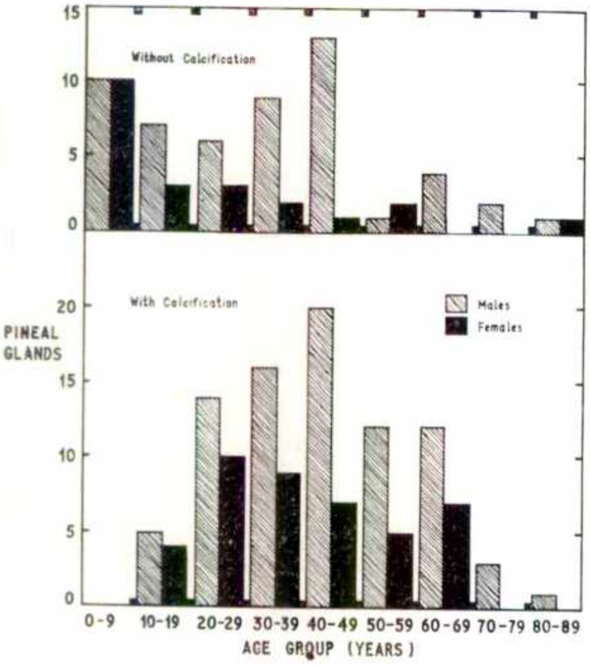


Table IV summarizes the percentage of degree of calcification in all decades in relation to sex and compared to the number of calcified pineal glands and to the total number of pineal glands. From this it is evident that the pineal glands in females are more heavily calcified than in males, 21 per cent to 12 per cent for Degree III among all calcified glands and 16 to 7 per cent for Degree III if compared with the total number of pineal glands examined. If the sexes are not considered and the degree of calcification is compared with the total number of pineal glands the following results are obtained: 25 per cent for Degree I, 33 per cent for Degree II and 10 per cent for Degree III. In other words 32 per cent of all pineal glands excluding the first decade are free of calcification (Degree 0) and 57 per cent (Degree 0 plus Degree I) are likely to be inapparent on a clinical radiograph. Up to 43 per cent (Degree II plus III) are likely to be detected in a skull radiograph.

To check objectively whether this type of staging of PGC is useful both authors had skull X-rays performed with the four pineals shown in Fig. 1 superimposed. The routine X ray apparatus of Mulago Hospital was used for this purpose. The pineals were placed on the X-ray film cassette marked by pins. The heads of the authors were superimposed and X rayed in posterio-anterior way, but a higher kilovoltage than routinely used was given (see Material and Methods). The X-ray film was developed in an automatic developing machine used for all the X-ray films at Mulago Hospital. Figure 3 demonstrates that Degree II and Degree III were detectable by ordinary X-ray techniques.

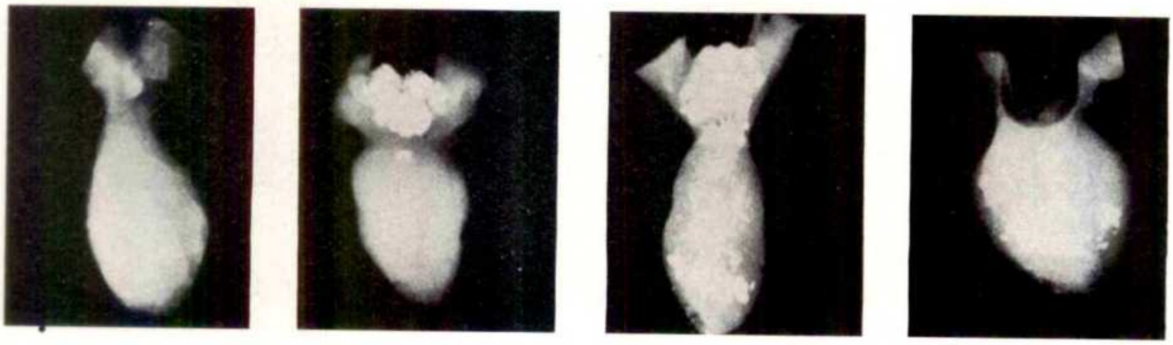


FIG. 2.

Type of calcification in pineal glands (from left to right).
1. No calcification in gland or in stalk.
2. Marked stalk calcification.
3. Marked stalk and gland calcification.
4. Marked gland calcification alone.

DISCUSSION

Our results, excluding the first decade of age, prove that in Black Africans pineal gland calcification (PGC) occurs in 68 per cent and that according to our staging 43 per cent should be radiologically detectable. This is in sharp contrast to the figures reported for non-white races such as Africans from Nigeria, 5·04 per cent (Daramola and Olowu, 1972), Black Americans from the United States, 9·8 per cent, but there was only 16 per cent in Whites in this series (Adeloye and Felson, 1974), Fijians, 15·6 per cent (McKay, 1973), Indians 11 per cent (Pillai, 1968) and 19·2 per cent (McKay 1973) as well as Japanese, 9·9 per cent (Chiba and Yamada, 1948).

The present results truly represent PGC because the glands have been isolated and the meninges have been stripped off before X raying; therefore confusion with other intracranial calcifications or superimposed meningeal concretions around the pineal can be excluded. Our staging method of the degree of PGC has been checked with a superimposed African skull and proved to be acceptable. However, a higher kilovoltage than used routinely had to be given and this might explain some of the low yields in the above quoted series, particularly since some of these studies were retrospective (Daramola and Oluwu, 1972) and since they did not indicate radiological data (Daramola and Olowu, 1972; McKay, 1973; Adeloye and Felson, 1974). It seems therefore, that PGC should be a useful diagnostic aid for the detection of intracranial space-occupying lesions in Black Africa if it is correctly looked for. Considering the ever-increasing number of road accidents and other craniocerebral trauma in African developing countries, a simple skull X ray should be carried out before one considers other

TABLE III

The degree of calcification of 125 pineal glands in relation to age and sex.

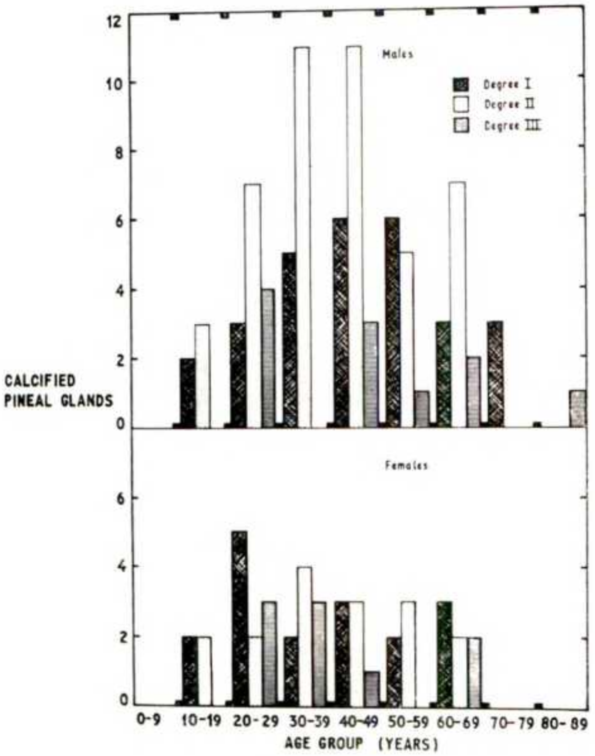
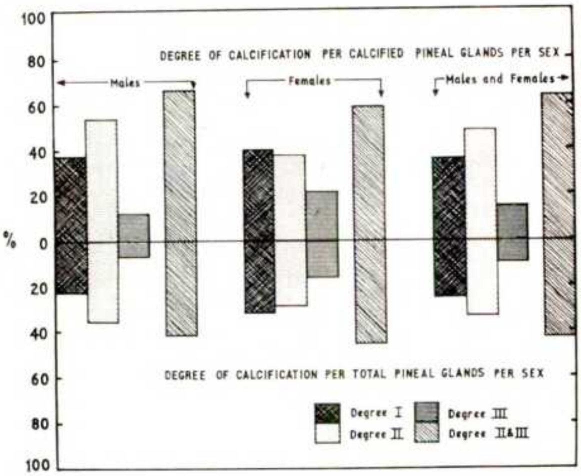


TABLE IV

The percentage of the degree of calcification per sex and per calcified pineal glands (above) and per total pineal glands (below) for all age groups excluding the first decade.



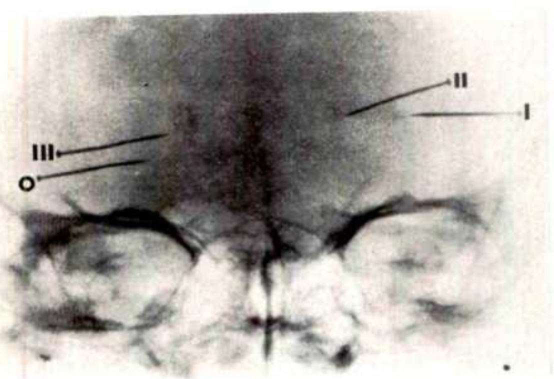


FIG. 3.

Skull radiograph of one of the authors (S.G.M.) with the four pineal glands shown in Fig. 1 superimposed and marked by pins. Degree II just recognizable and Degree III definitely visible (detail).

radiological procedures which often means transporting the patient over a long distance to a well-equipped centre. In the present series and elsewhere (Adeloye and Felson, 1974) no PGC was found in children below the age of ten although Schey (1974) found them twice and Peterson and Kieffer (1972) reported up to 5·1 per cent PGC in children. The present findings suggest that most calcifications occur by the third decade and that there is a sex difference, the pineals of females being more often calcified. The latter finding contrasts with the absence of PGC in females of the fourth decade (Daramola and Olowu, 1972) and the equal sex distribution in the white and black Americans (Adeloye and Felson, 1974).

PGC did not interfere with pineal gland function as evidenced by biochemical (Wurtman *et al.*, 1964) and histological studies (Wildi and Frauchiger, 1965). The significance of the stalk calcification with a male sex preference in this series is not clear, but such calcification is of equal value in clinical localization (McRae, 1965).

PGC also occurs in *pineal tumours* (Case records 1974; Komrower, 1974) and can be of diagnostic value; however it was absent in an ectopic pinealoma (Cohen *et al.*, 1974), and in a metastasizing pinealoblastoma (Banderjee and Kak, 1974).

Human pinealomas of the destructive type are known to be associated with a delayed menarche in girls and the functional type is associated with precocious puberty in boys, thus pointing to a sex-related function (Russel and Sachs, 1943; Netter, 1965; Cole, 1971; Komrower, 1974). However, Cole (1971) postulated that the critical site of involvement for premature puberty occurring in pinealomas appears to be in the posterior part of the hypothalamus and this has been confirmed by a clinicopathological study (Soas, 1967).

Studies on human pineal glands drew attention to its *weight* and possible relationship to malignancy (Rodin and Overall, 1967; Tapp and Blumfield, 1970) but the results are contradictory. The first authors found that the pineals were larger and heavier, whereas Tapp and Blumfield (1970) found that the weights were lighter in malignancy. Tapp and Huxley (1971) listed the weights of pineal glands in humans, not affected by malignant disease. If the mean cube roots of pineal weights for all ages and all cases of these three studies (5·1 for Rodin and Overall, 1967; 5·4 for Tapp and Blumfield, 1970; 5·4 for Tapp and Huxley, 1971) are compared to the present series (4·1) it is evident that the pineal glands of Ugandan Africans are lighter than those of Caucasians. However, the four studies agree that the weight of the pineal glands is maintained into old age. Tapp and Huxley (1971) found that the pineal glands of females below the age of 60 years were considerably heavier than those of males, they suggested that this fact could be explained by their higher calcium content. The present study similarly confirms that the pineal weight of females during their reproductive age is heavier than in corresponding males and that the degree of calcification is more marked in females.

The physiology of the pineal gland in animals and in man has caught considerable interest and the subject has recently been reviewed (*Lancet*, 1974). It appears that experimentally, the pineal gland of rats is partly a light-dependant organ which is biochemically depressed by light and activated by darkness (Klein and Weller, 1970). The production of melatonin in rats (pineal hormone) persists in continuous darkness but is suppressed by continuous light exposure (Ralph *et al.*, 1971). Abundant light exposure interferes with the pineal function and results in diminution in pineal weight in rats (Fiske *et al.*, 1962).

In addition there is now good evidence for an antigonadotropin effect of the pineal gland in male hamsters (Reiter *et al.*, 1970; Eichler and Moore, 1971) and in female rats (Dickson *et al.*, 1971; Vaughan *et al.*, 1971; Ota *et al.*, 1971).

Melatonin-excretion studies in man confirmed a circadian pattern (Lynch *et al.*, 1974) thus suggesting a light dependency. The influence of light in depressing the pineal weight could explain the low weights in this series as sun exposure is more regular on the equator than in temperate climates.

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1976, *British Journal of Radiology*, 49, 600–603

"Vascular" cerebral infarctions demonstrated by serial gamma-camera scinti photography

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ABSTRACT

The apparently paradoxical appearance of increased vascularity appearing in the radionuclide angiographic studies of a patient with cerebral infarction has recently been described and attributed to the "luxury perfusion syndrome". It is suggested that this phenomenon occurs more frequently than previously thought and in fact has been observed in nine patients presenting for a cerebral scan during a ten-month period. These cases are reviewed and an alternative explanation for the occurrence of increased vascularity on the dynamic study is submitted.

A recent case report by Snow and Keys (1974) describes serial changes in the circulation demonstrated by rapid-sequence radionuclide angiography in a patient with right middle cerebral artery occlusion. They noted in this patient that there was initial decrease in flow through the middle cerebral artery on the right when the study was performed at 24 hours. However, when the study was repeated at ten days a marked area of hyperaemia was observed over the right middle cerebral territory. At 23 days the dynamic scan had returned to normal. They ascribed this sequence of changes to the rare radionuclide demonstration of the "luxury perfusion syndrome" and reviewed the literature on the subject.

It is our experience that increased vascularity in an area of cerebral infarction demonstrated by radionuclide angiography is a well-established phenomenon. In a review of 1,000 consecutive cerebral scans over a ten-month period we have demonstrated it on nine occasions in patients with a proven cerebral infarction. Each patient was studied with a Nuclear Chicago Pho Gamma III or IV scintillation camera with a 4,000-hole low-energy collimator. The dynamic studies were recorded on a 35 mm film using a time-lapse camera or a microdot imager. In all nine cases increased vascularity was noted within five to 14 days of the establishment of the stroke.

In five cases cerebral angiography confirmed a cerebral infarction and in another patient a cerebral infarction was found at craniotomy as the diagnosis was in doubt. The remaining patients followed a clinical course typical of a cerebral infarction. In four of the nine cases a repeat study at 20 to 30 days revealed reduced perfusion through the appropriate middle cerebral artery in comparison with a normal study.

The following two cases illustrate a fairly typical sequence of events similar to that described by Snow and Keys.

Case 1

A 54-year-old male with a past history of hypertension presented with a severe left hemiparesis of stuttering onset five days after suffering a minor head injury. Because of the possibility of a chronic subdural haematoma, a scintigram was performed ten days after admission. The static study (Fig. 1B) showed a large area of increased isotope accumulation in the territory of the right middle cerebral artery typical of a cerebrovascular accident. The dynamic study (Fig. 1A) showed this to be vascular. Angiography demonstrated blockage of several branches of the right middle cerebral artery. The patient clinically improved and the brain scan was repeated three weeks later. A dynamic study now revealed reduced perfusion through the right middle cerebral artery (Fig. 1C). The static study was similar to that previously described.

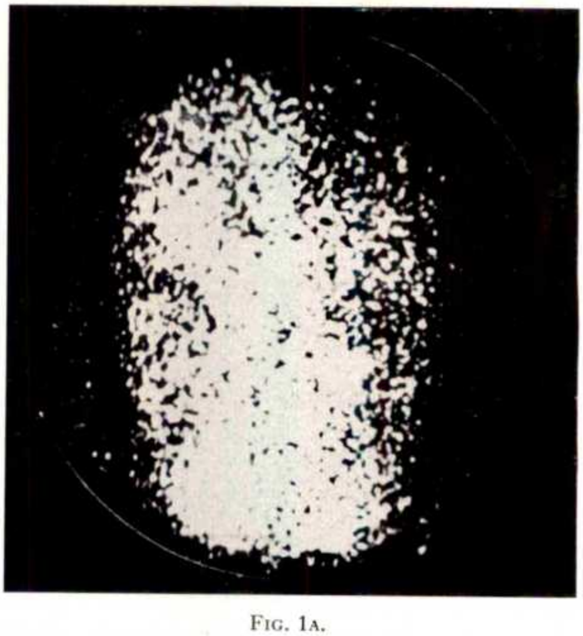

FIG. 1A.

Anterior three-second dynamic view of cerebral circulation taken from 35 mm film of 54-year-old male showing increased flow through the right middle cerebral artery ten days after the onset of a severe left hemiparesis.

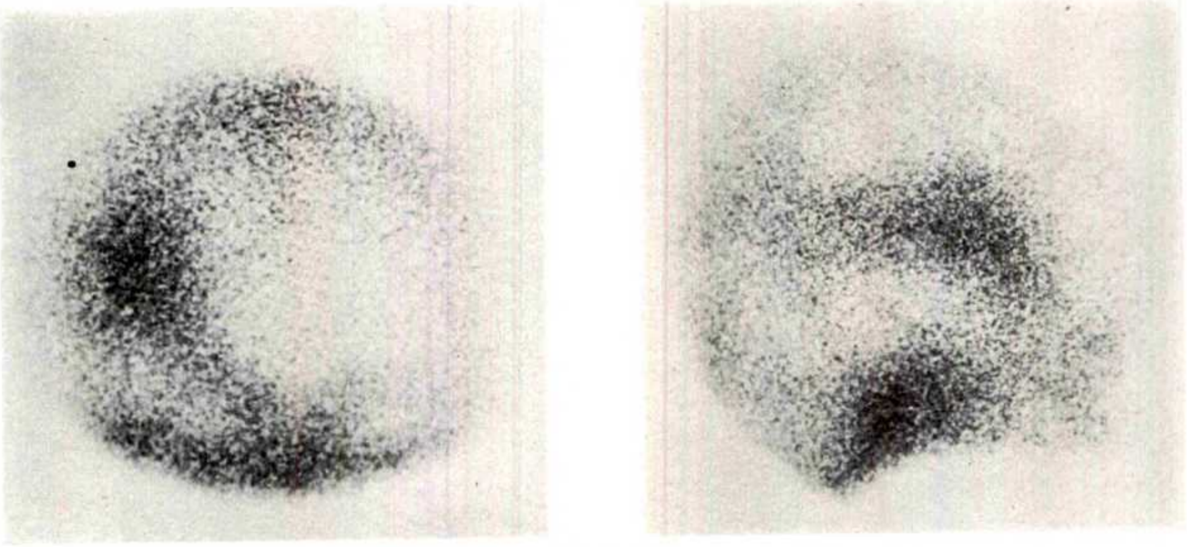

FIG. 1B.

Static views, anterior and right lateral, of same patient showing a diffuse area of increased isotope uptake typical of a middle cerebral infarction.

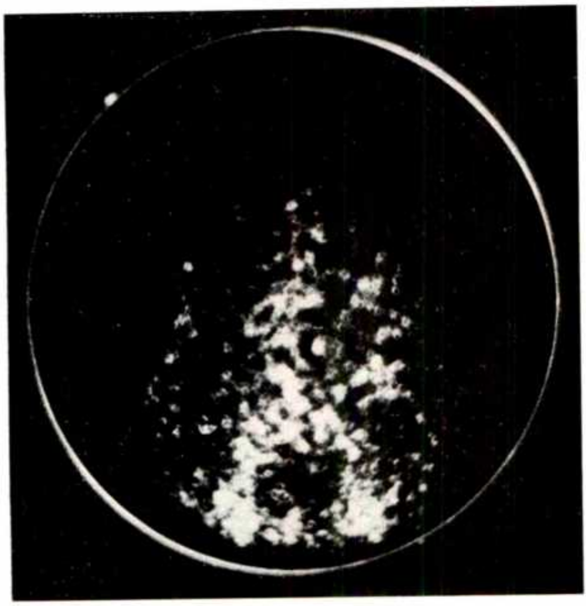

FIG. 1C.

Anterior three-second dynamic view of the same patient 31 days after admission showing reduced flow through the right middle cerebral artery.

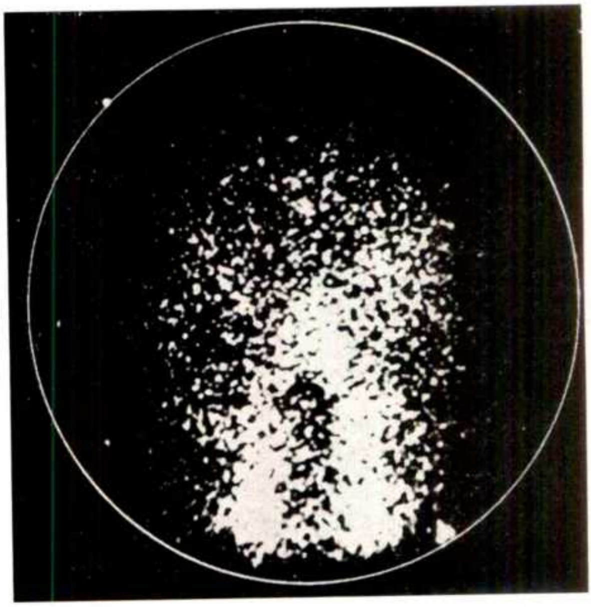

FIG. 2A.

Anterior three-second dynamic scan of 72-year-old man five days following a right hemiparesis showing increased flow through the left middle cerebral artery.

Case 2

A 72-year-old man with a past history of hypertension was admitted with gross dysphasia and a dense right hemiparesis. A scintigram done five days after admission revealed abnormally increased radionuclide distribution over the territory of the posterior branches of the left middle cerebral artery (Fig. 2B). The dynamic study (Fig. 2A) showed early increased vascularity over the left hemisphere. The patient clinically improved and a repeat study 27 days later (Fig. 2c) now revealed reduced flow through the left hemisphere, although some late vascularization was noted. After three months the neurological signs had almost completely resolved, but the patient suffered a fatal myocardial infarction.

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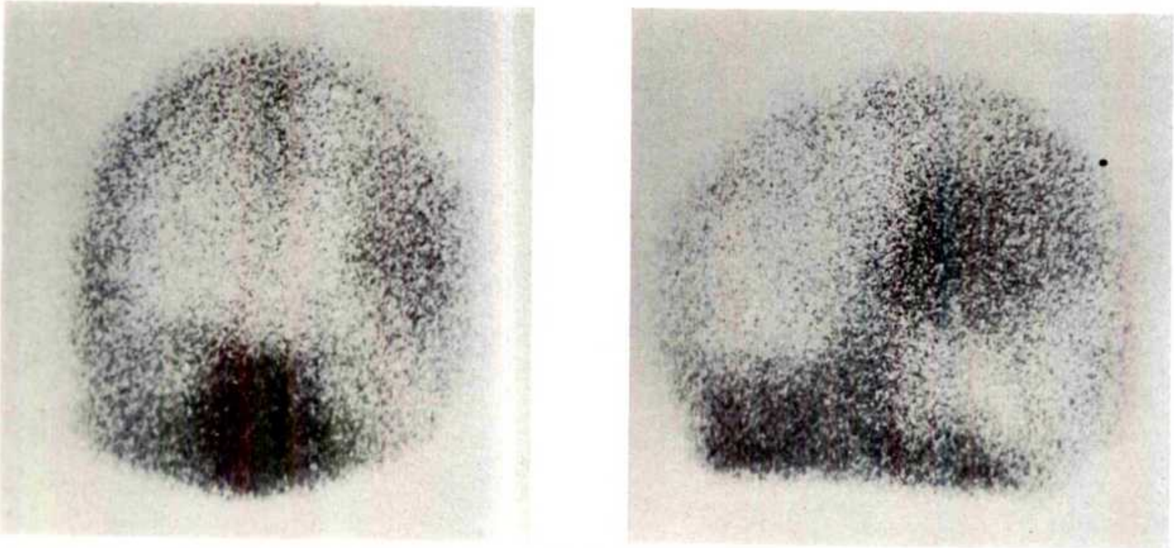

Fig. 2b.

Anterior and left lateral views of the same patient showing a diffuse area of increased isotope uptake over the posterior branches of the left middle cerebral artery.

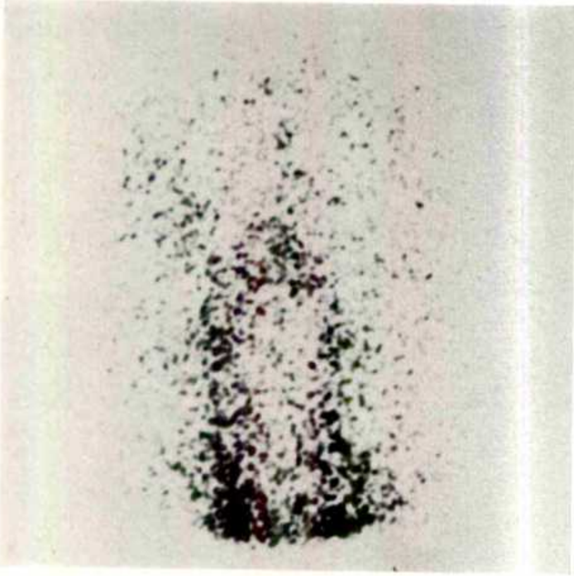

Fig. 2c.

Anterior three-second dynamic taken with a microdot imager showing absent flow through the left middle cerebral artery 32 days following the onset of a right hemiparesis.

Discussion

It is our experience that increased vascularity in areas of cerebral infarction is a definite phenomenon. However, we disagree with the explanation of Snow and Keys that the appearance is due to the "luxury perfusion syndrome". In his original description of the "luxury perfusion syndrome" Lassen (1966) described it as an over abundant cerebral blood flow relative to the metabolic needs of brain tissue. If pulmonary function is normal the condition is characterized by an unusually high saturation of the cerebral venous blood, and therefore bright red venous blood is a cardinal feature of the syndrome. Lassen quoted experimental work in dogs which showed that a period of hypoxia is followed by a reactive hyperaemia lasting some hours, much longer than would be needed to reoxygenate the brain. He proposed that the syndrome was due to the disturbance of the normal autoregulation of blood flow around an area of ischaemia produced by an acute metabolic acidosis.

If we in our dynamic studies are in fact noting the occurrence of the "luxury perfusion syndrome" the question must be asked as to why we do not view the phenomenon in every major cerebrovascular accident at an early stage. Certainly in our experience we have never viewed it before five days. The "luxury perfusion syndrome" as classically described should become obvious within minutes of a cerebral ischaemic insult. A possible explanation is we are not in fact viewing the luxury perfusion syndrome at all, and the term is a misnomer when applied to radionuclide angiography.

Standard texts of pathology describe in detail the resolution of a cerebral infarct. At approximately days three to five, the times when we have first noted the phenomenon of increased vascularity, there is an acute inflammatory reaction around an area of cerebral infarction. This inflammatory reaction is accompanied by an infiltration of scavenger cells and the rapid growth of a plethora of small blood vessels moving into the infarcted tissue from the periphery. This reaction reaches a maximum around 14 days. From 14 to 20 days the vessels tend to disappear and as the infarct is absorbed it becomes closed off by a wall of dense glial tissue. The time of disappearance of the blood vessels corresponds to the time of loss of vascularity as noted on the dynamic scan. Our view is that although we may be looking in a sense at "luxury perfusion" we are not observing the classical syndrome as previously described, but are in fact observing increased circulatory flow through inflamed tissue.

However, regardless of the explanation of this phenomenon we feel that a vascular appearance of a cerebral infarction as demonstrated on radionuclide angiography may be more common than previously thought. We certainly concur with the view of Snow and Keys that physicians should be aware of its occurrence in order that diagnostic confusion will not occur and a cerebral infarction be mistakenly reported as a vascular tumour.

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Book review

Non-invasive Brain Imaging: Computed Tomography and Radionuclides. Edited by H. J. de Blanc, jun., and J. A. Sorenson, pp. 220, 1975 (New York, The Society of Nuclear Medicine Inc.), £11·95.

Methods to demonstrate the brain and the pathological processes which affect it have been actively sought since the early days of radiology. Over the last decade radioactive isotope imaging of the brain has flourished. Its low cost and non-invasive nature have helped to make it a valuable diagnostic tool in a wide range of clinical conditions. A high false-negative rate has led to expressions of concern about the value of static imaging as a screening procedure. More recently computer analysis and dynamic studies have been employed. The advent of a non-invasive X-ray transmission technique, computer-assisted transverse axial tomography, however, has changed dramatically the clinical management of patients with neurological disorders—that is to say in those centres fortunate enough to be able to exploit the method.

Non-invasive Brain Imaging is a small volume from the United States, published by The Society of Nuclear Medicine. It presents a semi-didactic discussion by acknowledged American experts of techniques and current concepts in the rapidly developing fields of transverse axial computerized reconstruction related to both X-ray transmission and radioactive isotope emission methods. It also attempts an assessment of their relative clinical roles. In the former it fulfils a useful function presenting simply and clearly the background, limitations and possible future developments. In the latter all the contributors are hampered by the preliminary nature of their studies but all present well reasoned and scientific arguments indicating the clearly changing emphasis in neuroradiological investigation.

Two chapters are devoted especially to considerations of the blood/brain barrier and new developments with short-lived radio-pharmaceuticals.

It might be construed that some of the related discussion was influenced by territorial claims of differing medical disciplines. What seems important to this reviewer is whether a diagnostic procedure influences medical management and materially benefits the patient. No-one with any experience of computer tomography and the EMI-Scanner would doubt that.

I. Isherwood.

1976, *British Journal of Radiology*, *49*, 604–611

Computerized axial tomography: estimation of spatial and density resolution capability

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ABSTRACT

The spatial and density resolution capability of the EMI-Scanner device for computerized axial tomography has been determined *in vitro*. For density differences greater than ±1 per cent the spatial resolution is 6×6 mm. For density differences of 3 per cent and greater the resolution is 3×3 mm. Density resolution is at least ±1 per cent for objects greater than 1 cm. Preliminary data on *in vitro* measurement of X-ray linear attenuation coefficients in tissue biopsies and standard solutions are given, together with the early results of enhancement of tissue density differences *in vivo*. Implications of this new technique for an *in vivo* neuropathology are suggested.

The idea of obtaining more useful information from X rays in medical diagnosis than that achieved by single-shot transmission photography was first suggested by Bocage (1922) who introduced the concept of tomography. As perfected by Ziedses des Plantes (1932) this technique gave better resolution of deeper structures but being limited by the resolution capacity of photographic emulsions, could not display structures having small differences in density. A significant advance in tomography was also made by Di Chiro (1963) using this technique for pneumography of the brain in the axial transverse mode. This limitation on the amount of data obtained by X-ray techniques using film was first surmounted by Cameron and Sorenson (1963) who introduced the use of a collimated crystal detector system to measure the transmission of the photon beam directly in order to calculate and display the linear attenuation or so-called absorption coefficients§ of the tissues of the wrist, primarily to obtain quantitative data on the mineral content of the bones. This technique was further refined by Evens *et al.* (1968) who added a digital computer for calculation and display of the mineral content in integral units which could be reliably converted to grams of bone mineral/cm length of bone. This technique did not display the morphology of the structures scanned and has essentially been limited to bone scans of the foot and wrist (Goldsmith *et al.*, 1971).

A major advance was achieved when the tomographic technique in the axial transverse mode was combined with the photon transmission measurement principle in a new device designed by G. Hounsfield of the E.M.I. Company (Hounsfield, 1973). Initial studies with this instrument (the EMI-Scanner) at Atkinson Morley's Hospital in London have established the reliability of the method in displaying the morphology of tissue structures in the head, greatly facilitating the non-invasive diagnosis of brain disease (Ambrose and Hounsfield, 1973; Ambrose, 1973). Subsequently, Baker *et al.* (1974) in Rochester and New *et al.* (1974) in Boston have made further contributions based on their experience in the U.S.A. In order to test the density and spatial resolution capacity of this technique we have recently completed three series of experiments utilizing *in vitro* and *in vivo* methods. This is a preliminary report of these data; full details of our methods and the results will be published separately. McCullough *et al.* (1974) have recently completed a quantitative and radiologic study of this device at the Mayo Clinic.

METHODS

The claimed resolution of this apparatus was summarized by Hounsfield (1973). Print-out values related to linear attenuation coefficients are referred to the value for water being zero. On an expanded scale, the machine resolution is approximately one digit which is consistent with an integer print-out. Because the X-ray transmission measurements are obtained from intersecting beams spaced approximately 3 mm apart, the spatial resolution of the machine is, in principle, a 3 mm spot. Depending on density contrast and the size of the target, this resolution may, however, be degraded by a factor of 2 due to a target being partially in each of several display matrix elements. For example, if the matrix array of calculated absorption values for a small high-density target were geometrically designed so that a 3×3 mm target fell completely within one display matrix square (best case) then one square would show the total difference of that high-density target. If, on the other hand, the same target happened to fall centred on the intersection of four display squares, only a squarter of the target would fall in each element and hence a 6×6 mm area would be shown as increased in calculated density. In addition, the algorithm for calculating absorption values produces some slight smoothing between calculated elements of differences. Therefore, some machine smoothing of the edges of the calculated absorption within the array will reduce resolution from the theoretical limit of 3×3 mm.

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§The term "absorption" coefficient is used here instead of the physically correct term "linear attenuation coefficient".

The ability to determine density differences of small targets depends somewhat upon their size while the ability to resolve small targets spatially depends upon their density difference from surrounding materials. It was therefore important to determine the practical limits of the "trade-off" between these two factors determining the resolution capabilities of this technique. We also sought to determine the absorption characteristics of specific tissues in order to validate the diagnostic capacity of the technique and establish an *in vitro* method for quantitative calibration of absorption values of normal and abnormal tissue components. In order to achieve these aims, measurements were carried out on calibrated resolution targets and tissue biopsy samples (obtained at surgery and post-mortem) in two specially constructed phantoms, named respectively PADD-Y and PADD-X. The resolution targets consisted of 3×3 mm (in cross-section) sticks of epoxy-resin doped with varying percentages of calcium which produced linear absorption coefficients ranging from 0·018 to 0·037 mm^{-1}; this corresponded to a range of absorption values for the

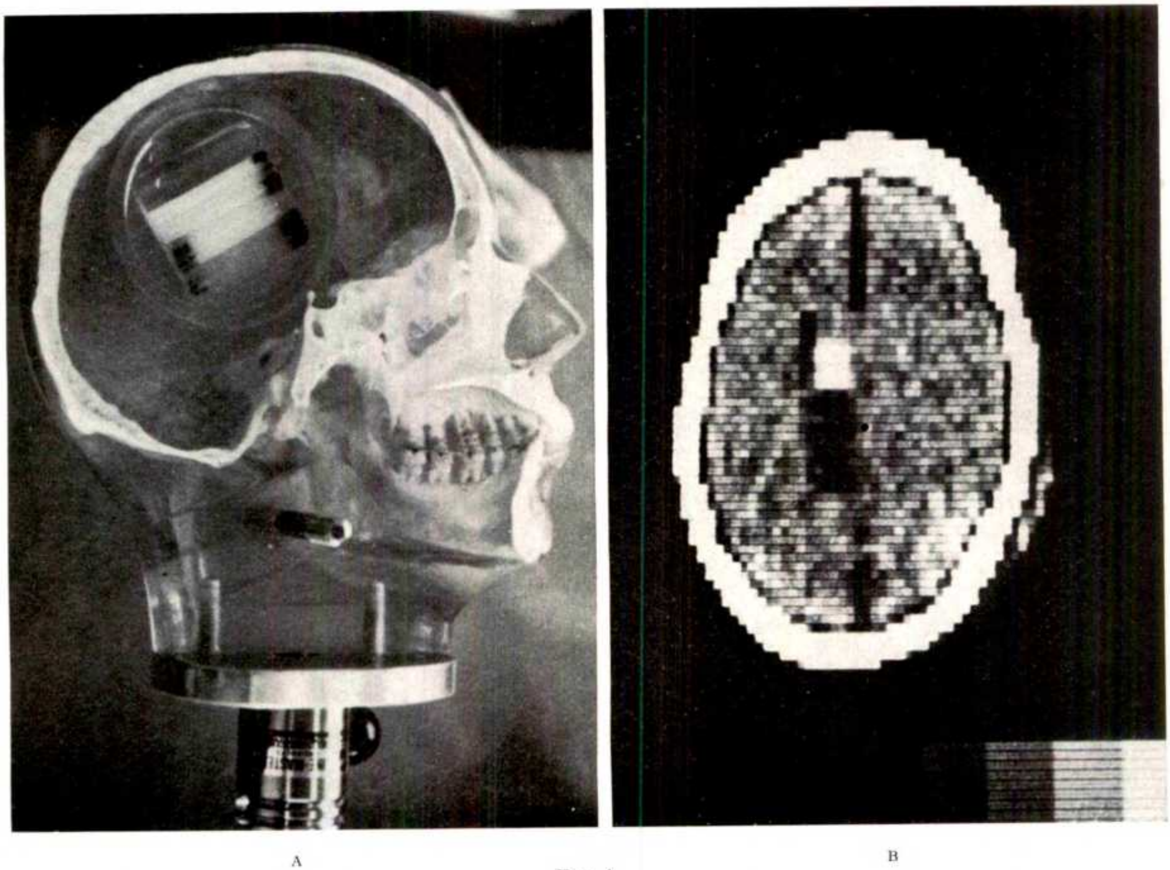
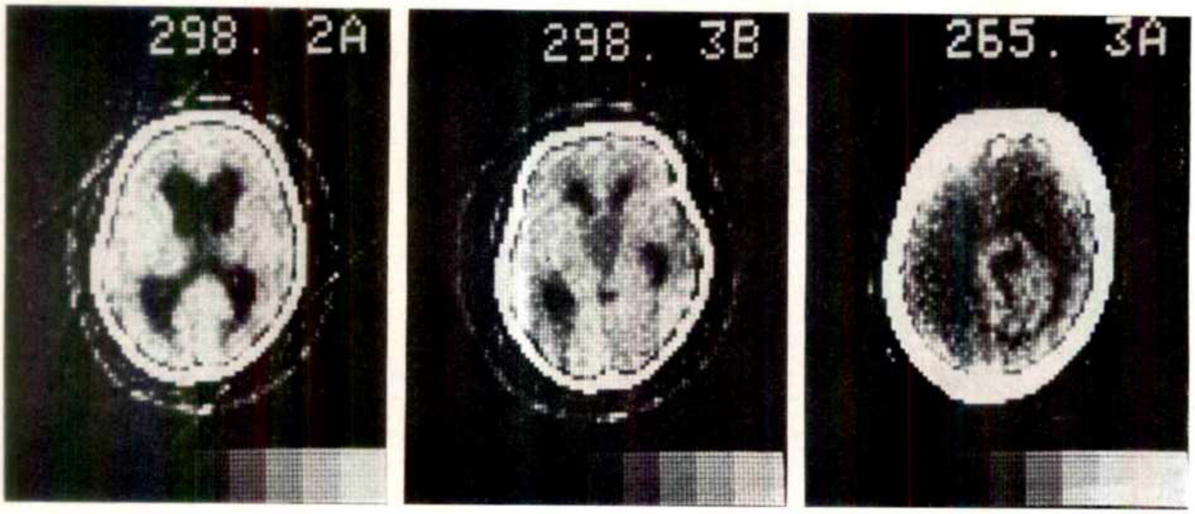


FIG. 1.

Views of X-ray Phantom with axial tomographic scan of phantom containing spatial and density resolution targets.

(A) Median plane of PADD-Y phantom showing insert.

(B) Scan of PADD-Y phantom showing relative densities of stick targets in place.

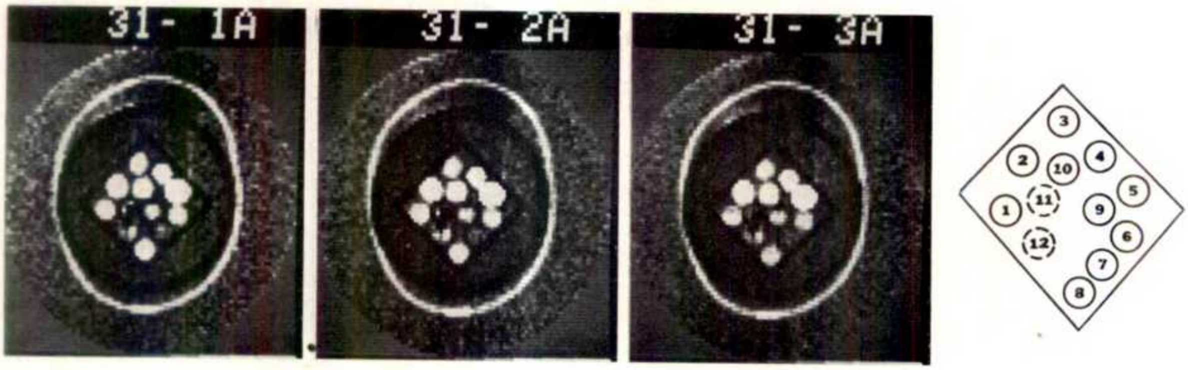


A B C

FIG. 2.

Scans of three patients with various lesions. Note the clear delineation of the cerebrospinal fluid in the ventricular cavities, the slightly greater density of the cystic craniopharyngioma contents compared to the CSF and the mixed high and low density zones of the glioblastoma. (A) Hydrocephalus. (B) Cystic craniopharyngioma. (C) Glioblastoma with cyst.

BIOPSY MEASUREMENT



EXPERIMENT NO. 31 31 MAY 1973

PADD - X

31 - 1A - 100 KV/40mA

31 - 2A - 120 KV/32mA

31 - 3A - 140 KV/27mA

50% Values at 100 KV

1. Citrated Blood = 9
2. Clotted Blood = 26
3. Meningioma = 6 (4 Days in N. Saline)
4. Meningioma (M.P.) = 20
5. 1.2% NaI = 100
6. 1.0% $CaCl_2$ = 6
7. Haematoporphyrin = 0
8. Conray 420 0.02% = 9
9. Pituitary Cyst Fluid = 2
10. Subdural Haematoma Fluid = 11

11. } Air Bubbles Invalidate { 11. Glioma
12. } Measurement { 12. N. Brain

FIG. 3.

Scans of PADD-X Phantom (a polyethylene bowl filled with water containing polyethylene vials for test samples) taken at three X-ray exposure ranges as shown. The relative positions of the numbered vials are shown in the diagram at upper right and the absorption coefficient values of their contents are given below.

EMI-Scanner between −50 and +420. In the first series of experiments, these density targets as well as solutions containing known amounts of calcium, sodium or iodine were placed inside PADD-Y, a suitably compartmented resin-filled human skull shown in Fig. 1.* Stacking of the 3 × 3 mm sticks in various arrays within the test cavity of the phantom and filling all interstices with mineral oil allowed the creation of targets with a spatial resolution of 3 mm on a side and with variations of absorption coefficient as small as 0·0002 mm^{-1} at the low end and 0·001 at the high end. In addition, solutions of three significantly absorbing elements (calcium, sodium and iodine) at closely spaced concentrations were also tested by filling special "tube" cavities in the phantom test module. Because the plastic material of PADD-Y had an absorption value approximately 10 per cent greater than that of normal brain tissue, additional noise was introduced into the calculated density values as explained below. To eliminate this noise we made a second phantom PADD-X, a polyethylene bowl filled with water. In addition to the calcium impregnated targets described above, this phantom could contain a large number of polystyrene vials which served as convenient containers for the various specific solutions mentioned above as well as tissue specimens obtained at surgery and at post-mortem examination

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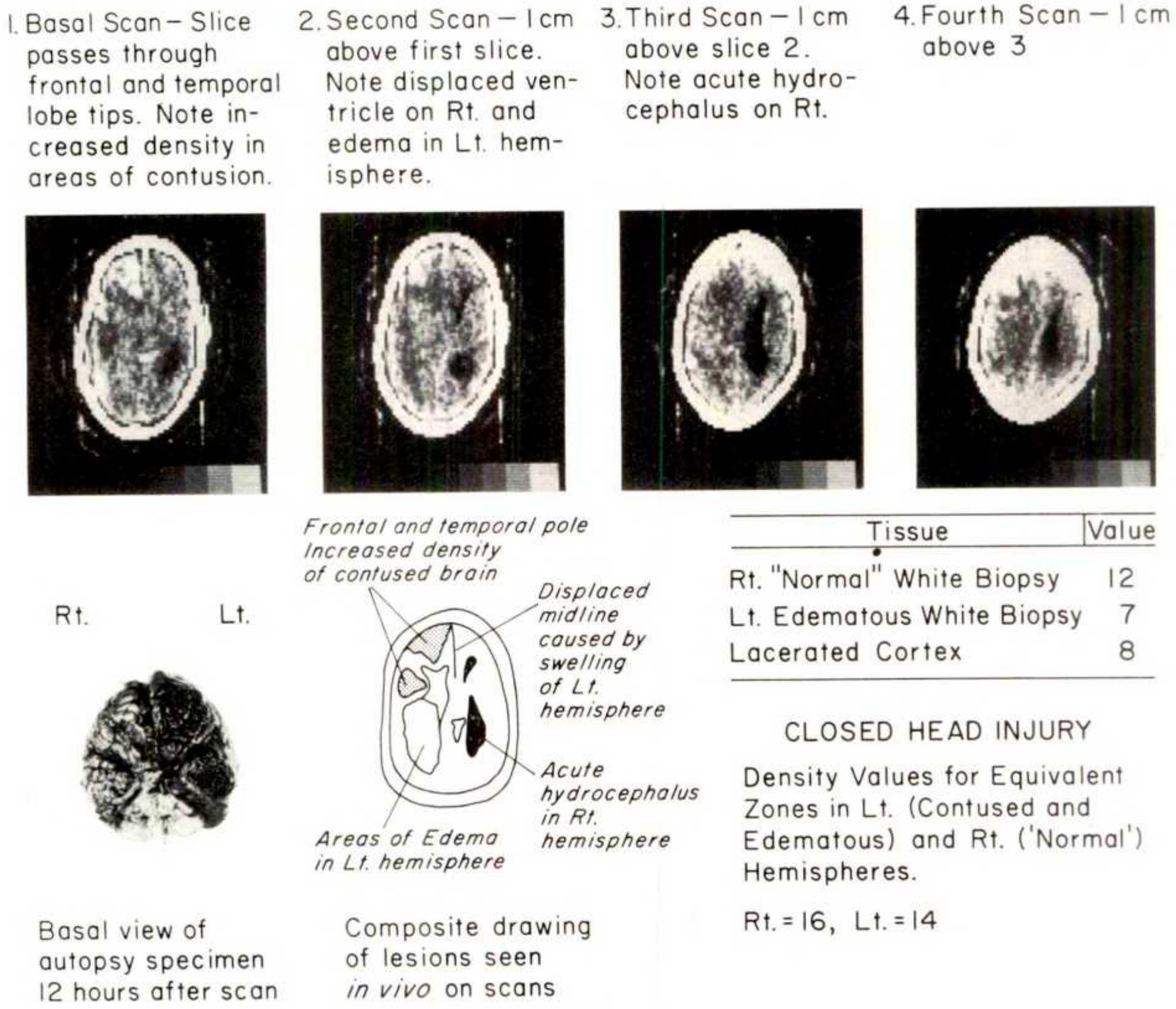
*3-M Skull Phantom, No. 74–300–1–0001–8.



1. Basal Scan – Slice passes through frontal and temporal lobe tips. Note increased density in areas of contusion.
2. Second Scan – 1 cm above first slice. Note displaced ventricle on Rt. and edema in Lt. hemisphere.
3. Third Scan – 1 cm above slice 2. Note acute hydrocephalus on Rt.
4. Fourth Scan – 1 cm above 3
Rt.
Lt.
Basal view of autopsy specimen 12 hours after scan
Frontal and temporal pole Increased density of contused brain
Displaced midline caused by swelling of Lt. hemisphere
Acute hydrocephalus in Rt. hemisphere
Areas of Edema in Lt. hemisphere
Composite drawing of lesions seen *in vivo* on scans
Tissue | Value
Rt. "Normal" White Biopsy 12
Lt. Edematous White Biopsy 7
Lacerated Cortex 8
CLOSED HEAD INJURY
Density Values for Equivalent Zones in Lt. (Contused and Edematous) and Rt. ('Normal') Hemispheres.
Rt. = 16, Lt. = 14

FIG. 4.

Four successive scans displaying four adjacent axial tomographic slices obtained in a head injured patient who subsequently died. The basal view of the brain at autopsy is also shown and density values obtained from various zones are given.

of patients with a variety of cerebral lesions. Finally, the digital print-out data on 300 patients examined at Atkinson Morley's Hospital were reviewed.

RESULTS

Figure 2 shows three axial tomographic views of the brains of three patients with different diagnoses as shown. Apart from the striking clarity of soft tissue and lesion depiction, it will be noted that there is a black border just inside the skull segment. Our first experiment with PADD-Y showed that this black zone does not represent a low-density area of the subarachnoid space, as it is clearly seen also in the axial tomograph of PADD-Y shown in Fig. 1. Because this phantom consisted of a human skull completely impregnated in plastic with no surface subarachnoid space on the "brain", the black zone must be a machine artifact. It is the result of the algorithm used to calculate the absorption densities; attempts within the program to smooth between abrupt density transitions resulted in an overshoot at the borders reminiscent of the traditional mach band effect. The overshoot at a step change is of the order of 3 per cent of the difference in density on either side of the step and persists for approximately 1 resolution element corresponding to 3 mm. This 3 per cent overshoot is not noticeable on small density changes between resolution elements.

The quality of spatial and density resolution achieved is also demonstrated in Fig. 1. A bar pattern resolution target was formed with the calcium impregnated sticks. The illustration shows what was also verified from the digital print-out, namely that line targets of 3 mm size can indeed be resolved. The bars of decreasing percentages of calcium from top to bottom are separated by sticks of polystyrene 3 mm wide which has an absorption value about 50, 5 per cent lower than the 2 per cent calcium carbonate sticks. This density difference was clearly seen, even on the Polaroid print of the CRT display. Similar experiments were conducted with the PADD-X phantom which provided satisfactory confirmation of these resolution characteristics (Fig. 3).

Preliminary analysis of these data showed that for density differences greater than ±1 per cent the spatial resolution achieved was at least as good as the theoretical value of a 6 mm square. For targets with density difference of 3 per cent and greater we found that a 3×3 mm target was discernible by eye. For target dimensions of 10 mm or greater we found that density differences of about 1 per cent could be measured reliably. This was in good agreement with the theoretical signal-to-noise of 1 per cent which should be achieved for large regions of homogeneous tissue (1 cm+). The edge effects for sharp boundaries of significant density difference were also found to be in agreement with theoretical values. Boundaries were accurately given in space to ±1 resolution element (±3 mm) but the absolute values for density on either side of these boundaries were smeared for up to ±1 additional resolution element (±3 mm) in either direction. In the optimum condition of the PADD-X phantom the signal-to-noise and hence the absolute values of measured densities were well within the theoretical range and density differences of ±1 per cent were reliably measured when averaged over the 10 mm cross-section of the vials containing our test solutions (Fig. 3).

Our second series of experiments consisted of measurements of absorption values for specific tissues using the PADD-X phantom. Figure 4 shows the scan of a patient who had suffered a severe head injury and died within 24 hours after trauma from irreversible cerebral oedema in one severely contused hemisphere. Also shown in this figure is a basal view of the autopsy specimen along with values of grossly oedematous and contralateral normal white matter obtained in the PADD-X phantom. The correspondence between locations of contused and oedematous brain in the scan and the

TABLE I

ABSORPTION VALUES MEASURED BY COMPUTERIZED AXIAL TOMOGRAPHY*

Normal brain tissues	
White matter	=10–19
Grey matter	=17–26
Cerebrospinal fluid	= 2–6
Calcification in choroid plexus and pineal gland	=45–65
Abnormal brain tissues	
Oedematous white matter (head injury)	= 4–8
Periventricular plaque (multiple sclerosis)	= 7–11
Haemorrhagic contusion (head injury)	=11–14
Brain tumours	
Meningioma	=6–20 (most values lay between 16–20)
Medulloblastoma	=9–12
Glioma	=7–14 (Astrocytoma grades III and IV)
Standard solutions	
Calcium carbonate 1%	=19
Calcium carbonate 5%	=48
Calcium lactate 4%	=7
Sodium iodide 0·1%	=9
Sodium iodide 1·2%	=100
Sodium iodide 12%	=500+

*Arbitrary units related to water=0 (range of values obtained).

autopsy specimen are clearly evident. Table I and Fig. 5 summarize our preliminary data on the absorption coefficient values obtained by this technique for various chemical solutions and tissues as measured within PADD-X phantom in the EMI-scanner apparatus.

A third set of experiments were conducted to evaluate the use of intravenously administered agents for enhancing the density differences between normal and abnormal tissues in the brain. This was based on an observation made by one of the authors (J. Ambrose) that when a scan was done after carotid angiography a previously poorly visible lesion on an earlier scan became clearly distinguishable due to increased density within the abnormal zone. Conray "420" (sodium iothalamate) in a dose of 10 ml. was given intravenously to a series of patients in whom previous scans had shown a cerebral tumour. Repeat scans were obtained four to six hours after the injection. Figures 6 and 7 show scans taken

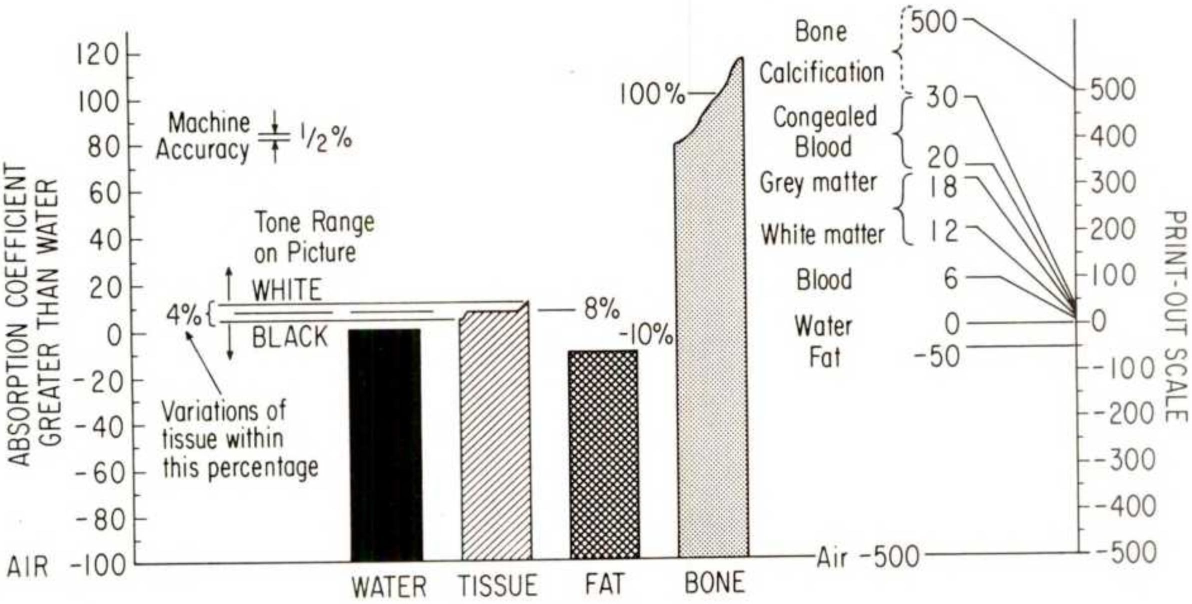


FIG. 5.

Diagrammatic summary of density resolution capability for tissue of the head in the EMI-Scanner apparatus. Note that all values for X-ray absorption are relative to water = 0.

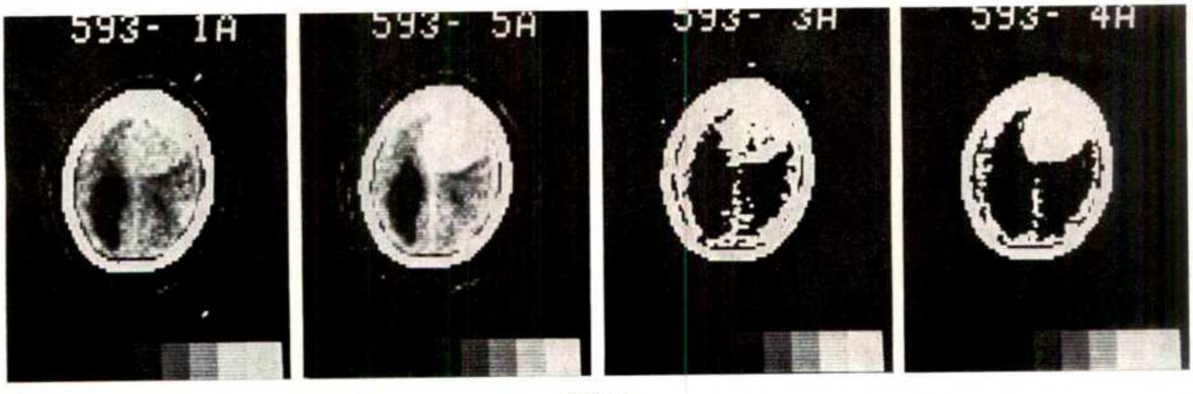
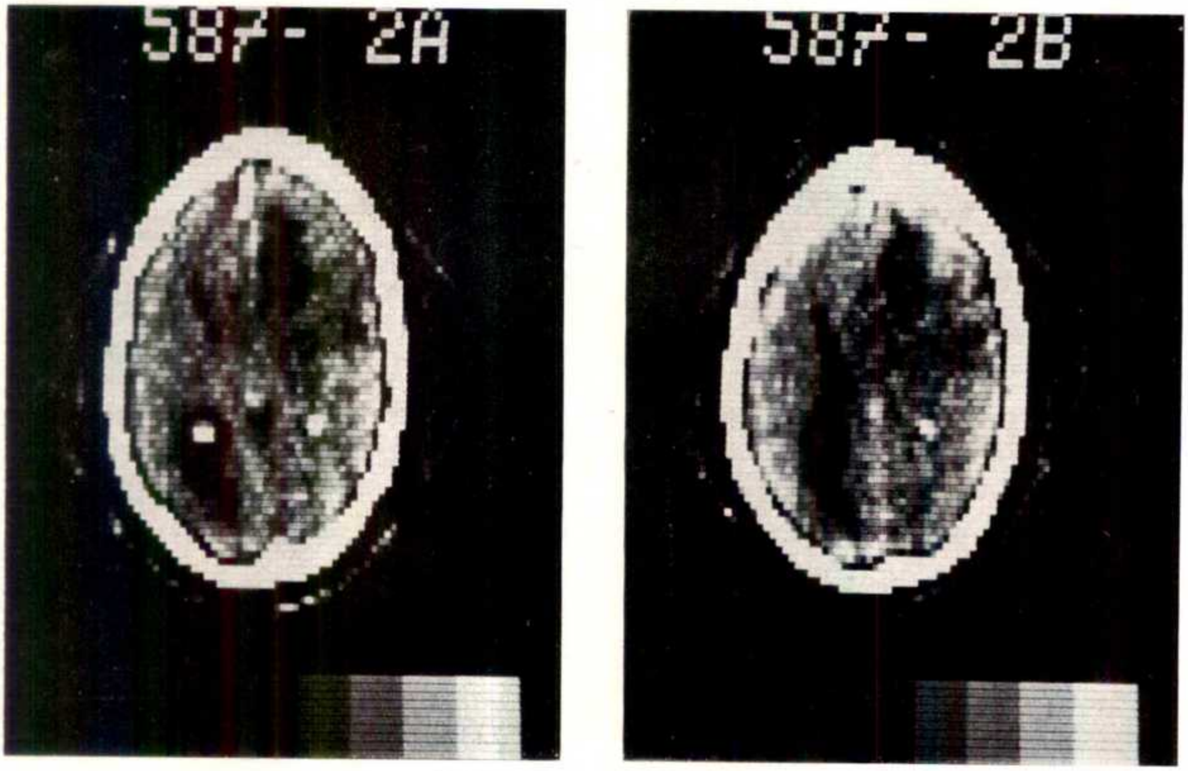


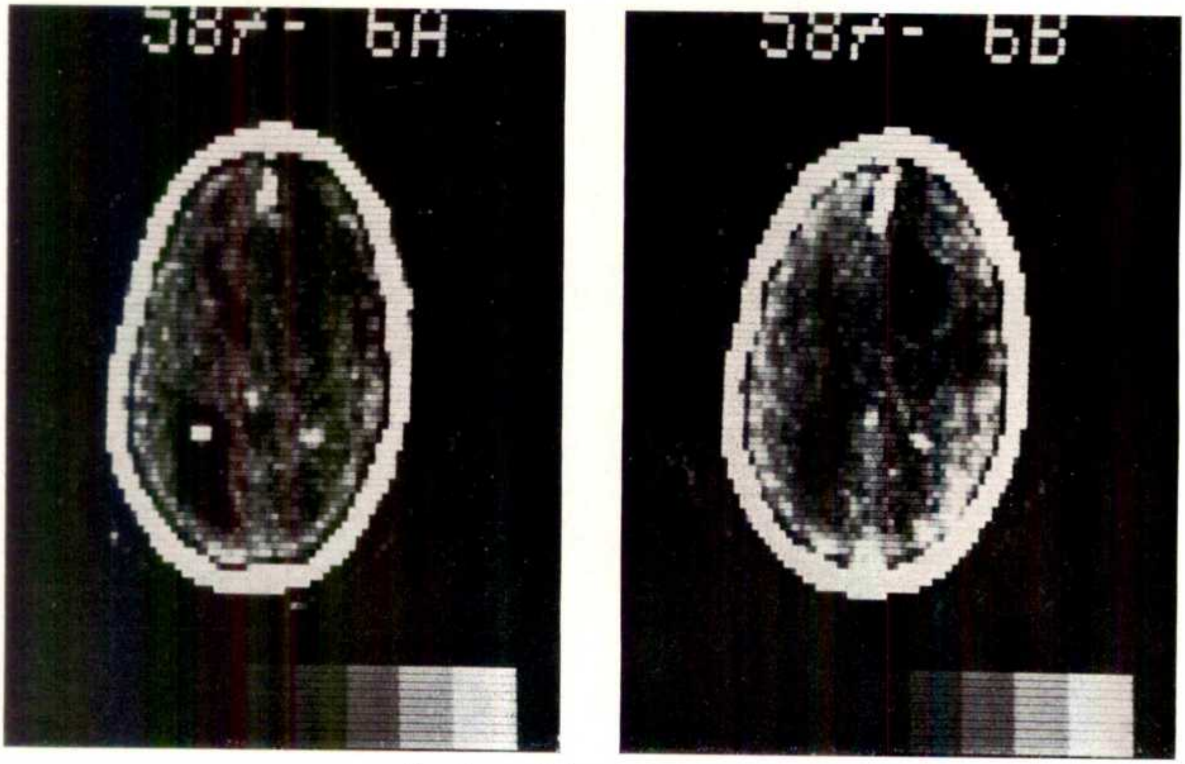
FIG. 6.

Scans taken at one identical level in a patient with an anterior falx meningioma showing the density enhancement produced by previously administered Conray "60". The two views on the right were obtained with the device set for manual measurement of the absorption coefficients.

Patient J.D. Rt. frontal astrocytoma (III).



Before Conray 120 kV 32 mA.



After Conray (5½ hours) 120 kV 32 mA.

FIG. 7.

Scans at two identical levels in a patient with a right frontal malignant glioma taken before and after 10 ml. of Conray given intravenously. Note the absence of significant contrast enhancement as noted in Fig. 6.

before and after the injection of Conray. Note the marked enhancement of lesion density in Fig. 6 (meningioma) as compared to the visibly insignificant changes seen in Fig. 7 (glioma). Although further observations in a larger series of cases are required, our preliminary review of these data suggested that lesion density enhancement (up to 23 per cent) was prominent in benign, well vascularized lesions (meningiomas and low grade gliomas) but less obvious in malignant lesions (astrocytomas grades III and IV).

Discussion

We are satisfied that the technique of computerized axial tomography can provide significant advantages in non-invasive diagnosis and serial evaluation of neural disease. Preliminary analysis of our data has confirmed the claimed spatial and density resolution characteristics of this device within the limits described. The necessity of surrounding the scanned object in a water-bath obviously limits the EMI-Scanner as presently constructed for an extension of this technique to other parts of the body. McCullough *et al.* (1974) have presented a theoretical argument for the necessity of the surrounding water to reduce inaccuracies and obtain consistent interpretation of the attenuation coefficients. It remains to be demonstrated therefore whether further technological advances will obviate such limitations to computerized tomography.

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Radiation doses to staff in a department of nuclear medicine

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ABSTRACT

A survey of data concerning radiation protection of staff working in the Nuclear Medicine Department and associated sections of the Physics Department at the Royal Marsden Hospital (Surrey Branch) is given for the period 1972 to 1975 inclusive.

Results of routine film monitoring and whole-body counting are presented. Additional film monitors were used to check working areas, finger doses and any discrepancies between doses to the upper and lower trunk of personnel.

In general, exposure to staff in the Nuclear Medicine Department is below 220 mrad per person per year, and below 1,000 mrad per person per year in the Radioisotope Dispensary. The dose received by radiographers is primarily due to spending time close to patients. Since about 5,000 intravenous injections of radionuclides are given each year in our department, the resulting finger doses to the staff involved may give rise to concern unless the task is shared.

A great deal of attention has been paid in recent years to radiation protection in departments of radiotherapy and diagnostic radiology, and the doses received by personnel are well documented. There is much less information available regarding the effectiveness of radiation protection procedures in departments of nuclear medicine. In view of our rapidly-increasing patient load, we have examined data concerning radiation doses received by staff carrying out routine work in the Department of Nuclear Medicine and associated sections of the Physics Department at the Royal Marsden Hospital (Surrey Branch) in the four years from 1972 to 1975.

During this time, the number of medical and technical staff involved has increased from 13 to 20 and the total amount of radioactive material handled (excluding gynaecological insertions) has more than doubled. Figure 1 shows this in more detail. Both ^{67}Ga and ^{99}Tc^{m} have been used in sharply increasing amounts and we are now equipped with a 500 mCi ^{99}Tc^{m} generator renewed weekly. The decrease in use of other radionuclides is due largely to ^{99}Tc^{m} polyphosphate replacing ^{18}F for bone scanning. The peak at the beginning of 1973 coincides with the concurrent use of ^{99}Tc^{m} polyphosphate and ^{18}F for a period of comparison.

Beta-emitters are not used a great deal in the Nuclear Medicine Department. ^{3}H is never used, and ^{32}P only occasionally. Our routine personnel monitoring film is calibrated for both ^{32}P and ^{131}I.

METHODS OF MONITORING

Routine monitoring

Routine monitoring of all nuclear medicine staff (radiographers, technical and medical) is carried out by means of film badges which are changed monthly. In addition, since April 1973 personnel have worn separate film badges when working in the dispensary; these are read weekly.

The film badges used are of the type described by Spiegler and Davis (1959). These badges will record minimum doses of about 10 mrad in the high-energy range, and of about 5 mrad at 140 keV, the energy of ^{99}Tc^{m}. It is generally accepted that in routine use the overall accuracy with which the films can be interpreted is much improved if the energy of the radiation to which they have been exposed is known. Film badge readings reported here are given in terms of the surface dose (mrad) to all staff for each quarter.

Other methods of monitoring working surfaces and personnel are of a routine nature. Only a few, minor, incidents of contamination have been encountered, so these are not considered here.

Additional monitoring

On occasions specially prepared finger films were worn by medical staff when giving injections of radioactive tracers. The films, which are sensitive to both γ and energetic β radiation, were worn taped to the nail side of the finger. In our experience, this is the side on which the highest dose is recorded when giving injections.

In order to obtain information as to the variability of exposure over the surface of the body, radiographers have worn films at both breast pocket and waist level. There was up to 50 per cent variation of results on individuals, but no definitive pattern has been found.

Selected working areas were monitored by placing film badges in appropriate positions for two-week periods. The dose to staff at these locations was estimated on the basis of observed occupation.

RESULTS OF FILM BADGE MONITORING

1. *Radioisotope dispensary staff*

The total doses recorded per quarter by the film badges worn by radioisotope dispensary staff are

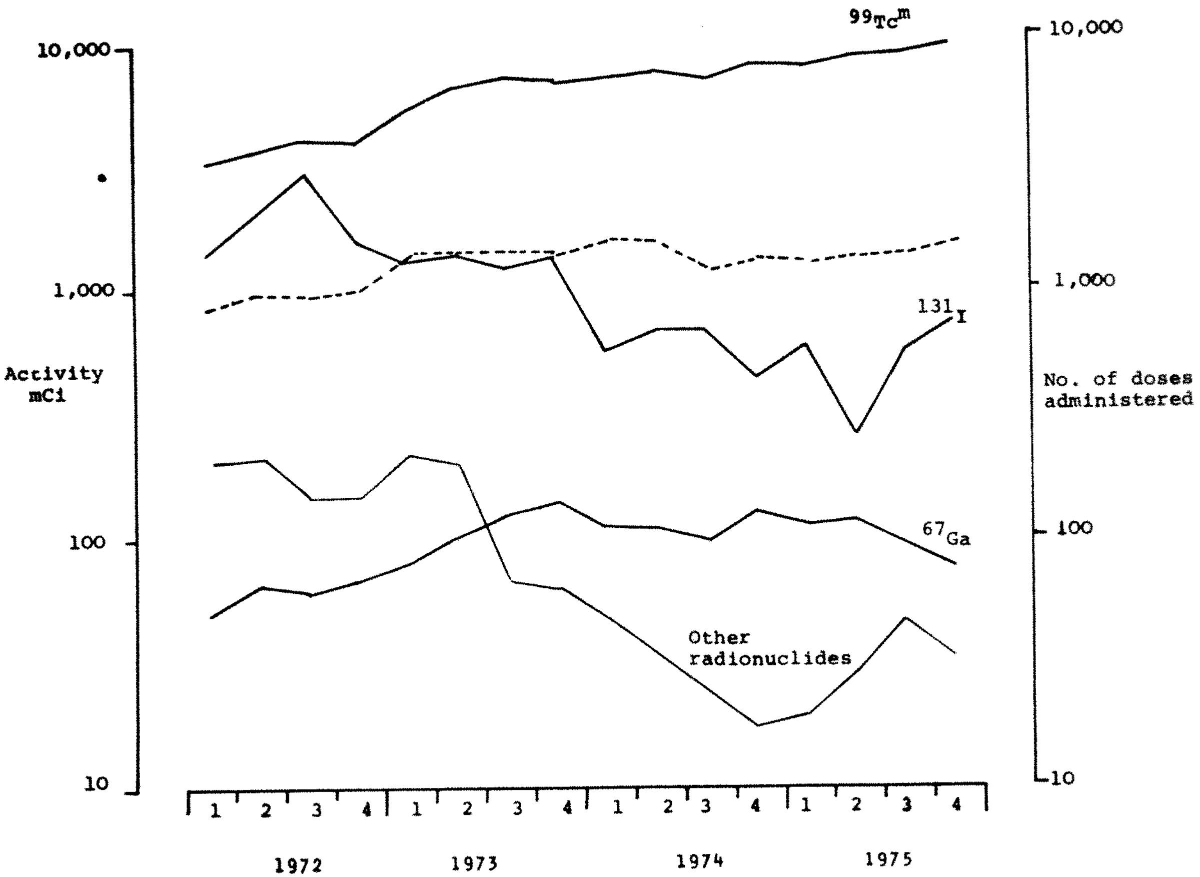

FIG. 1.

Activity (solid line) of various radionuclides administered per quarter, together with the number of tracer doses administered per quarter (broken line).

shown in Fig. 2. These data apply to two technicians who carry out the majority of the dispensing by alternate weeks, together with a small contribution from two other staff members who help out occasionally. The maximum dose for one month recorded by one person is 245 mrad. More usually, individual monthly doses of 50–100 mrad are recorded.

Film monitors placed in dispensing areas showed that routine dispensing accounted for a dose of about 5–10 mrad per week to the technician concerned. However, a dose of about 10–20 mrad may be received each week while setting up the new ^{99}Tc^m generator and dismantling the old one.

The time spent handling radionuclides in a typical week of dispensing during 1974 is shown in Table I.

Normally other laboratory staff, whose work concerns the preparation of such radiopharmaceuticals as labelled red cells and albumin and associated techniques, receive film badge doses less than 10 mrad per month and never in excess of 35 mrad per month.

2. *Medical staff*

This group comprises doctors and a nurse administering injections. We have been able to identify doses delivered to doctors solely due to their work in the Nuclear Medicine Department only since January 1973. These are shown in Fig. 3A. The number of people involved in this group fluctuated between four and six in 1973 and 1974. The results shown for 1975 refer to only two people, since no detectable exposure was recorded on monitors worn by three other doctors who gave injections only occasionally. The highest individual dose recorded in any one month was 74 mrad.

A summary of the finger film readings for four people giving injections is shown in Table II.

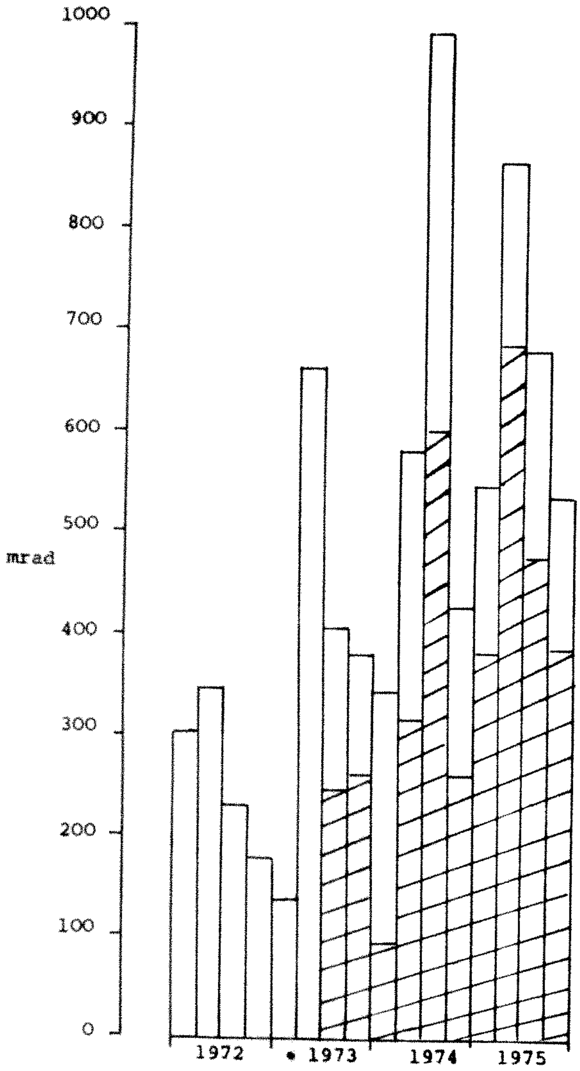

FIG. 2.

Total quarterly film badge readings for radioisotope dispensary staff. The shaded area represents readings from badges changed weekly and worn only while dispensing.

3. *Radiographers*

In this department, the radiographers' work consists almost entirely of *in vivo* scanning. They are not normally exposed to radiation until the tracer dose is administered to the patient who then becomes the main source of exposure.

Film badge results are shown in Fig. 3B. The number of radiographers involved ranges from three in the first five months of 1975 to a maximum of six in 1974. The highest individual dose recorded in any one month was 70 mrad, but is normally 20–40 mrad per month.

Film badges placed on the consoles of a gamma-camera and a rectilinear scanner each recorded a dose of less than 10 mrad over a two-week period. Working at the console of a scanner or camera thus accounts for only a small part of the exposure received. Table III gives an estimate of the exposure to the radiographers while in close proximity to the patient.

MEASUREMENTS OF BODY BURDENS

In addition to monthly film badge monitoring, since 1973 all staff in this study have undergone routine whole-body counting, in general at intervals of six months. Radioisotope dispensary staff are counted at intervals of three months.

The whole-body counter used is that described by Trott and Cottrall (1966). It consists of four sodium iodide detectors positioned two above and two below a couch on which the subject lies. The detectors are connected to a multichannel analyser which covers an energy range from 10 keV to 1 MeV. By using the summed output of all four detectors, the sensitivity of the counter is independent of source position to within 20 per cent.

The apparatus is calibrated using different isotopes contained in a whole-body phantom and is checked for drift with a ^{137}Cs source before each body burden measurement. A ^{99}Tc^{m} burden greater than 15 nCi can be detected quantitatively.

TABLE I

DETAILS OF ITEMS DISPENSED IN A TYPICAL WEEK DURING 1974

Nuclide	^{99}Tc^{m}	^{131}I	^{67}Ga	^{75}Se	^{51}Cr	^{123}I	*^{192}Ir	*^{111}In	*^{32}P
Time/week (min.)	230	70	50	30	15–20	10–15	30–90	10	5–10
Number of preparations	95	3–4	6	3	3–4	2	1	1	1

*These radionuclides are not dispensed every week.

Of the 120 measurements carried out between 1973 and 1975, 118 fell into the categories shown in Table IV. In the two remaining cases contamination activities of approximately 1 μCi were recorded. In the case of a doctor, the contamination was located on his hands after giving a series of injections of radioactive tracers. A laboratory technician had approximately 1 μCi of ^{99}Tc^{m} in her hair after her first week of radioisotope dispensing. She was recounted after washing her hair and the contamination was reduced to approximately 250 nCi.

However, all these doses are very low. In the worst possible situation where a burden of 100 nCi of ^{99}Tc^{m} is maintained in the thyroid for one year, it has been calculated that the dose to the thyroid is only about 2 rad. The maximum permissible annual dose to this organ is 30 rem.

DISCUSSION

The results presented suggest specific areas in which exposure to radiation is most likely to occur.

Routine work in the radioisotope dispensary will account for 60–120 mrad of the technicians' monthly dose. The dose received while setting up the new ^{99}Tc^{m} generator each week will vary between operators, and will depend on the type of generator used. This task should be carried out as quickly as possible, but working close to the column may be unavoidable if tubes for elution have to be attached to it.

TABLE II

RESULTS OF FINGER FILMS WORN BY MEDICAL STAFF

Position worn	Dose/100 injections (mrad)
Left thumb	140–300
Left middle finger	345–445
Right little finger	30
Right middle finger	100–342
Right thumb	100–690

Periods in which highest quarterly doses were recorded correspond to times when ^{192}Ir was being dispensed. Cutting wire into lengths and loading it into polythene tubing was often a long job, particularly when the apparatus was in the development stage. ^{192}Ir contributed significantly to the quarterly recorded dose during the periods April to September 1973 and June to September 1974.

In other periods when a high quarterly dose was recorded, there were several ^{131}I therapy patients, for example in the last quarter of 1973. Here dose is accumulated while monitoring the patients on the ward, and particularly when decontaminating the room and disposing of waste after the patient has been discharged.

Medical staff are exposed to unsealed sources containing mainly ^{99}Tc^{m} and ^{67}Ga when administering doses to patients by intravenous injection. They also take blood samples from patients who have received therapy doses of up to 150 mCi ^{131}I. These blood samples are first taken two hours after administration of the dose. The tracers used for injections are stored individually in lead pots behind shielding until required. The doctor then draws up the tracer into a syringe which is held in a stainless steel shield lined with up to 3 mm of lead. Our results on finger monitoring suggest that with our patient load, if one person were to give all the injections for a year, then the dose to the hands from handling loaded syringes and disposing of waste needles,

TABLE III

ESTIMATED DOSE TO RADIOGRAPHERS WORKING CLOSE TO PATIENTS

	Gamma-camera			Rectilinear scanner				
Type of scan	Liver	Brain	Bone	Brain	Thyroid	Pancreas	^{67}Ga whole-body	^{131}I therapy whole-body
Number per week	37	11–12	16	8	9	3	6	1–2 per month
Time per patient at couchside (min.)	2–3	3–4	6	10	2	3	10	5
Couchside dose (mrad/h)	0·4	1·2	1·8	1·2	0·5	0·5	0·5	15–20
Average weekly dose to radiographer (mrad)	0·8	1·0	3·0	1·6	0·2	0·2	0·5	2–3

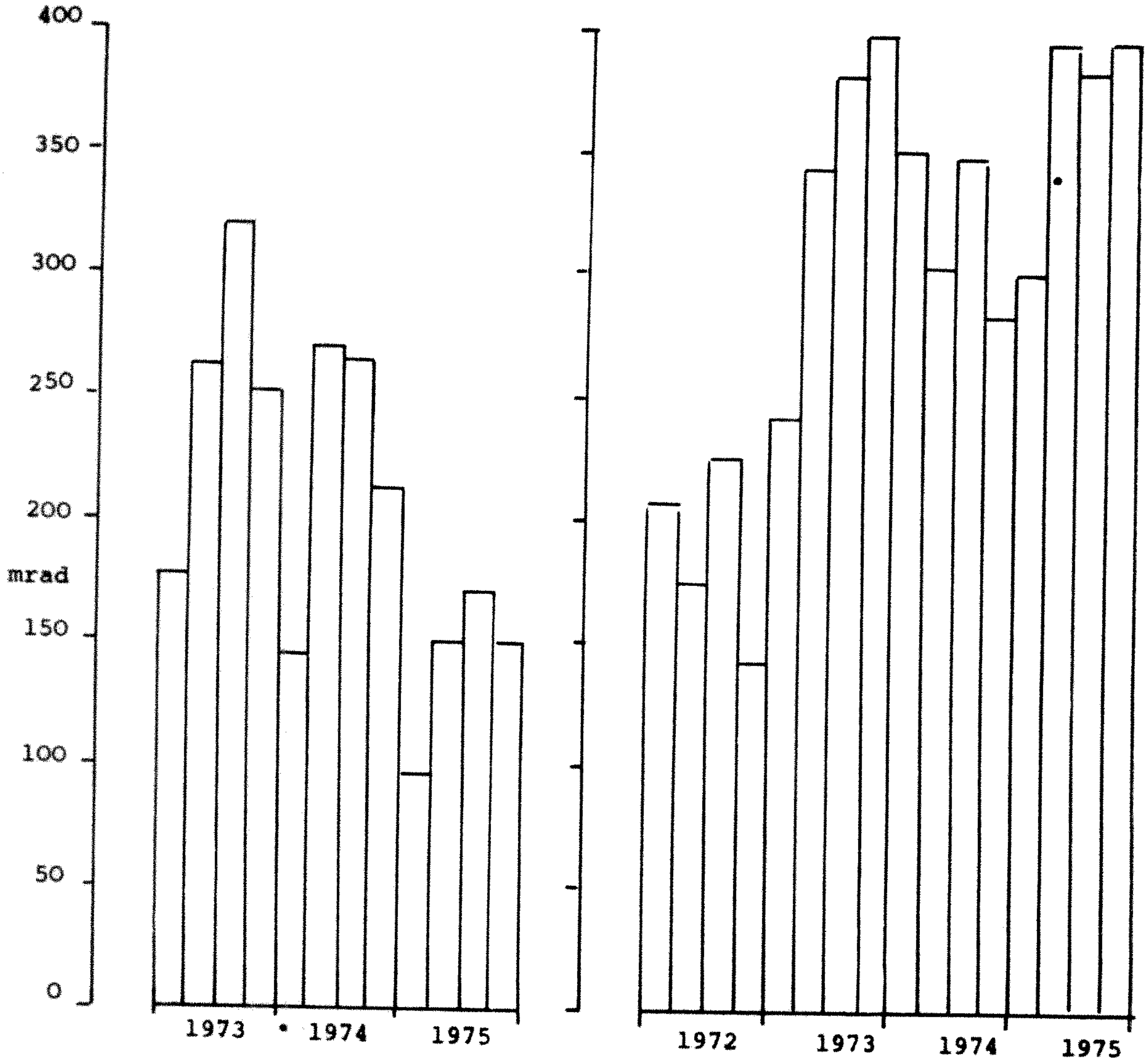

FIG. 3.

Total quarterly film badge readings for (A) medical staff and (B) radiographers.

TABLE IV

RESULTS OF WHOLE-BODY COUNTING

Designation of staff	Number of measurements with no detectable activity	Number of positive measurements	Isotope detected	Activity detected (nCi)
Radioisotope dispensary staff	23	6	^{131}I	6–60
		12	^{99}Tc^{m}	30–700
Other laboratory staff	19	7	^{99}Tc^{m}	30–100
Medical staff	9	16	^{99}Tc^{m}	30–100
Radiographers	15	11	^{99}Tc^{m}	10–300

swabs and syringes, would reach a level of 25 rem compared with the maximum permissible dose of 75 rem. Although this level is only one-third of the maximum permissible dose, in the event of a spill it could be raised considerably. In our opinion, unless exposure to the hands can be greatly reduced by better shielding design, we think it desirable that several people should share the task of giving injections.

Radiographers are primarily exposed when in proximity to patients containing radioactive material. The most probable source of exposure is when scanning ^{131}I therapy patients on the third day after administration of the dose. There are only one or two such patients each month, however, and there is no need for the radiographer to spend more than two or three minutes at the couch side with the patient. The maximum whole-body retention of ^{131}I with which a patient is scanned is 7 mCi. In this instance, the dose to a radiographer standing at the console, 1 m away from the patient, is 1·5 mrad/hour. Even a diagnostic X-ray screen placed between the patient and radiographer will reduce this dose to 0·5 mrad/hour.

Bone scans, of which there may be six in a day, are another potential hazard. Again, only a small proportion of the total scanning time is spent within 1 m of the patient, except in a few cases where the patient needs to be, of held if other techniques of immobilization are inappropriate.

The overall increase in total dose to radiographers is in part due to the increased patient load. Also, if two radiographers are working at one machine, both will be exposed to radiation. Thus the total dose to personnel will be reduced if there is only one person at a time working on each machine.

The most effective form of protection for a radiographer is to be close to the patient only when really necessary. Some new gamma-cameras can be operated by remote control so that the radiographer need not leave the patient's side during the examination. If this procedure were to become common practice, it could significantly increase the dose to the radiographer.

While the whole-body measurements showed no serious contamination of any member of staff, they do play an important educational role. Staff are kept aware of possible contamination situations.

CONCLUSION

It is clear from this study that there is no need for any member of staff in the Nuclear Medicine Department to receive more than a small proportion of the maximum permissible dose.

Nevertheless certain situations do call for particular attention.

An important factor in the exposure of radiographers is the time they spend in close proximity to each patient. Although this dose is at present small, it may increase with increasing patient load.

Similarly, the finger dose to doctors giving injections should be watched to ensure that there is no significant increase. New techniques to reduce this source of exposure should be considered.

ACKNOWLEDGMENTS

We would like to thank Dr. W. Anderson and the Radiation Protection Service of the Royal Marsden Hospital for their help. The staff of the Low Background Laboratory have been of great assistance in carrying out the measurements of whole-body burdens. We particularly acknowledge the willing co-operation of those members of the Nuclear Medicine and Physics Departments who are involved in routine work with radioisotopes.

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A comparison of clinical results in brain scanning using germanium semiconductor detectors and sodium iodide detectors

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ABSTRACT

A comparison is presented of the image quality obtained with a 70 mm Ge(Li) detector scanner and with routine techniques based on NaI (Tl) detectors. One hundred and sixty-five pairs of brain scans have been examined for which the patients have been scanned with both Ge(Li) and NaI (Tl) detectors. It is concluded that no major difficulties exist in introducing Ge(Li) scanners and that while a comparison of scans from different instruments is difficult there is evidence that improved diagnostic information may be obtained from scanners with Ge(Li) detectors.

Autopsy studies have demonstrated the large percentage of false negatives resulting from the interpretation of Technetium-99m brain scans, particularly of those with lesions in the temporal and midline regions (Krishnamurthy *et al.*, 1972). One factor limiting scan quality is the poor energy resolution of the NaI(Tl) detectors normally used. In consequence, the usual analyser window settings include a significant component of counts due to scattered radiation in the image. However, the development of lithium drifted germanium semiconductor detectors, which have excellent energy resolution, has reached the stage where planar detectors of 70 mm diamater suitable for use in medical radio-isotope scanning are becoming available.

The use of these large diameter Ge(Li) detectors in scanning should permit much more effective exclusion of scattered radiation, giving sharper scan images particularly in areas of adjacent high and low concentrations of radioactivity. More complex studies with multiple isotope imaging should also become more feasible. The physical characteristics of these detectors and some examples of their use in clinical trials were reported in an earlier paper (Glass *et al.*, 1972) and a number of other groups have published studies of the use of smaller Ge(Li) detectors (Beck *et al.*, 1972; Brill *et al.*, 1972; Hoffer *et al.*, 1971). The principal disadvantage found with the prototype detectors used in this study was their limited sensitivity; however, improved fabrication techniques should permit the sensitivity for Technetium-99m γ rays to be raised by at least a factor of two.

This paper presents a more detailed analysis of 165 brain scans made with a Ge(Li) detector scanner and with NaI(Tl) instruments. The conventional NaI(Tl) scans were made with either a 12·7 cm diameter detector Ohio Nuclear scanner or with a Nuclear Chicago gamma-camera. The results obtained with the Ge(Li) detector scanner are therefore being compared with scans as obtained routinely. A description of the equipment and an assessment of the relative performance of Ge(Li) and NaI(Tl) detectors of equal size was presented previously (Glass *et al.*, 1972).

MATERIAL AND METHOD

The Ge(Li) scans were performed using a Siemens collimator of focal length 13 cm and resolution 1·2 cm (FWHM). This collimator was chosen to give a suitable compromise between resolution and sensitivity. The Ohio Nuclear scans were made with a collimator of focal length 12·7 cm and resolution 1·4 cm. The Nuclear Chicago camera and collimator system used gave a resolution of 1·5 cm at 10 cm from the collimator face. The Ohio Nuclear scanner and Nuclear Chicago camera were operated with analyser windows set at 126–161 keV and 133–168 keV respectively while the Ge(Li) scanner windows were set to 136–144 keV.

About 25,000 or 50,000 counts were collected in

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the semiconductor brain scans while the Ohio Nuclear scans normally contained some 200,000 counts. The camera pictures typically contained 250,000 counts, many of which lie outside the brain region. It will be seen that the statistics of the semiconductor scans, imposed by the limit of an acceptable scanning time, restricted the image quality.

While the comparison of scans collected on three quite different machines is complex, it is felt that accepting the differences in conditions noted, together with possible uptake time variations, it is still possible to make a useful preliminary assessment of the place of a semiconductor scanner in routine brain imaging.

Four or five views of the brain were obtained on the NaI(Tl) rectilinear scanner or gamma camera. These were anterior, posterior, both laterals and vertex views. The scans were started one hour after injection of 20 mCi of ^{99}Tc^{m}-pertechnetate. Initially, the NaI(Tl) and Ge(Li) scans were done one and two hours respectively after injection of radioisotope. The sequence of scanning was randomized for the last 46 scans in the series to eliminate any possible bias in favour of the later examination. Lateral views only were obtained.

In detecting abnormalities the NaI(Tl) scans have the advantage over the Ge(Li) scans of extra views, and to avoid this only corresponding views from both types of scan were compared for analysis.

The scans were categorized as positive or negative with respect to abnormalities. In a few patients both types of scan showed the main "lesion" equally well but definite additional "lesions" were shown on only one of them. In the statistics, the latter was counted as a positive scan but the scan showing only the main "lesion" was counted as negative.

Where there were differences between the results of Ge(Li) and NaI(Tl) scans, the clinical histories were obtained together with the results of any further investigations.

If the abnormal scan fitted the clinical history, it was designated "appropriate", if not, "inappropriate". Where no clinical localizing signs were present, no such comments were made. If subsequent investigations confirmed the presence of a lesion, it was designated "confirmed correct", if the scan was proved wrong, "confirmed incorrect" and if no further investigations were done, the scan was designated "unconfirmed".

RESULTS

The results of the 165 sets of scans compared in this manner are summarized in Table I.

Positive scans

There were 20 positive NaI(Tl) scans and 31 positive Ge(Li) scans. Nineteen patients with positive NaI(Tl) scans also had positive Ge(Li) scans. The Ge(Li) scans were considered to have demonstrated the "lesion" more effectively in three of these (see Fig. 1). The 12 remaining patients with

TABLE I

ANALYSIS OF RESULTS

		NaI(Tl) scans	
		Abnormal	Normal
Ge(Li) scans	Abnormal	19	12
	Normal	1	133

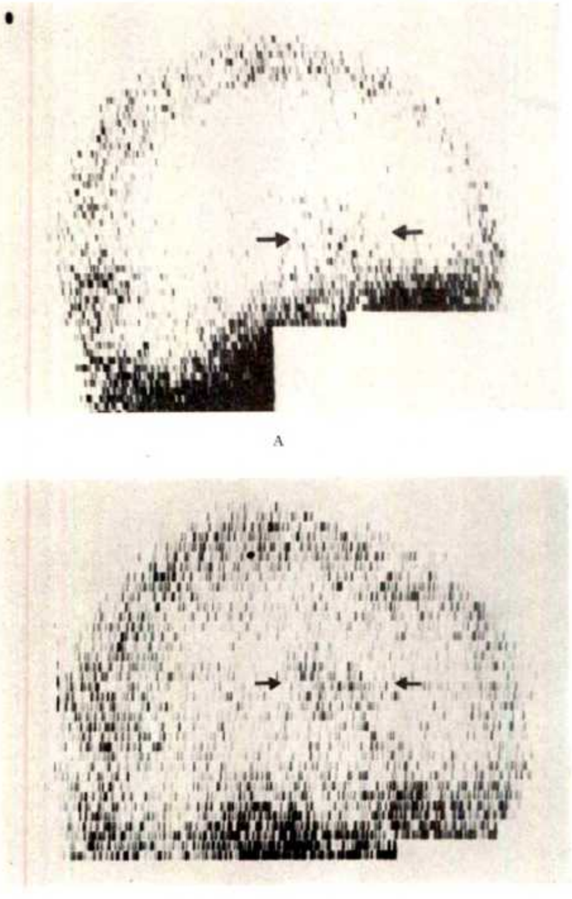

FIG. 1.

The NaI(Tl) scan shows a rounded area of increased activity merging with the activity at the base of the skull. In the Ge(Li) scan, this "lesion" is shown separated from the skull base by an area of normal brain. This appears to be due to the increased area of brain visualized as a result of the reduction of scattered radiation.

TABLE II

DETAILS OF CASES WITH POSITIVE GE(LI) SCANS AND NEGATIVE NAI(TL) SCANS

Patient	Ge(Li)	Clinical history	Remarks
1. D.M.	"Lesion" in right upper fronto-parietal area	Well controlled hypertension. Two years progressive left hemiplegia.	Appropriate, unconfirmed.
2. J.M.	Large "lesion" involving adjacent areas of L. fronto-parietal, temporal and occipital lobes. NaI(Tl) scan only showed equivocal lesion in left occipital lobe.	Hypertensive patient presenting with acute onset of disorientation, aphasia, amnesia and agnosia.	Appropriate, unconfirmed.
3. W.H.	Right lower frontal lesion.	Lung carcinoma treated ten years ago. Also longstanding epileptic. Anticonvulsant therapy increased in last year because of loss of control. Two months of personality change improved by reducing doses of drugs.	Appropriate, unconfirmed. Probable false positive.
4. L.F.	"Lesion" in left parietal area. This was equivocal on the NaI(Tl) scan.	Malignant hypertension with acute onset of right hemiparesis, hemianesthesia, 7th upper motor neuron cranial nerve palsy and dysphasia.	Appropriate, unconfirmed.
5. B.H.	Diffuse "lesion" in left frontal area.	Headaches and increased tendon reflexes in right arm three months after traffic accident. Improved with Ergotamine. No further investigation.	Appropriate, unconfirmed.
6. M.D.	Increased activity in right posterior fossa.	Breast carcinoma with cerebral metastasis. Signs of raised intracranial pressure. Vertebral angiogram: suspicion of right posterior fossa lesion. Local radiotherapy given with improvement.	Appropriate, confirmed correct.
7. D.W.	Large "lesion" high in left parietal lobe. Smaller "lesions" also noted in left parietal temporal and occipital lobes. NaI(Tl) scan showed only the large lesion.	Adenocarcinoma of lung treated three years ago. Progressive weakness in right arm with increased tendon reflexes. Carotid angiogram showed a large left upper parietal mass and multiple small masses in left temporal parietal and occipital lobes.	Appropriate, confirmed correct.
8. G.R.	Multiple small "lesions" over left fronto-parietal lobes.	Acute onset of fever, diarrhoea and drowsiness with an infected left eye. Developed acute renal failure. Treated with Cloxacillin and Ampicillin. Electro-encephalogram showed diffuse abnormalities. Cerebrospinal fluid was sterile. Gradual improvement. Right extensor plantar response noted later.	Appropriate, unconfirmed.

TABLE II (*continued*)

Patient	Ge(Li)	Clinical history	Remarks
9. S.J.	Left temporal "lesion". On NaI(Tl) scan, the "lesion" was ill-defined and merged with activity at base of brain (Fig. 1).	Carcinoma of left parotid treated with fast neutrons. One-and-a-half years later gustatory hallucinations, episodes of peculiar behaviour, papilloedema. Craniotomy and biopsy—radiation necrosis left temporal lobe.	Appropriate, confirmed.
10. A.W.	Three "lesions" in left parietal lobe.	Stiffness, numbness and weakness in right upper and lower limbs with upper motor neuron signs. Electro-encephalogram—"disturbance in left frontotemporal region. Probably a vascular lesion".	Appropriate, unconfirmed.
11. B.P.	"Lesion" in right fronto-parietal region (Fig. 2).	Attacks of numbness and clumsiness left hand; slight weakness left leg, slight apraxia. Probable transient ischaemic attacks.	Appropriate, unconfirmed.
12. M.S.	"Lesion" in right occipital region (Fig. 3).	Three weeks after renal transplant, persistent pyrexia, several grand mal attacks, confusion and decreasing consciousness leading to death. At autopsy, several small abscesses found in right occipital lobe.	Appropriate confirmed.

positive Ge(Li) scans had normal NaI(Tl) scans (see Figs. 2 and 3). Details of these 12 cases are given in Table II. One patient had a positive NaI(T1) scan and a negative Ge(Li) scan; however, the "lesion" was not confirmed and this was probably a false-positive NaI(Tl) scan. The abnormalities shown by the 12 Ge(Li) scans were compatible with the clinical histories. Five patients were considered to be suffering from cerebrovascular accidents and further investigations were not pursued. The patient with post-concussion headaches and increased right arm reflexes improved with Ergotamine and no further investigation was done.

Two cases (Patients 6 and 7) were later confirmed to be suffering from cerebral metastases which were not shown on the NaI(Tl) scans. Patient 8 was strongly suspected of having a septicaemia with possible small cerebral metastases in his left cerebrum. This was, however, not confirmed. The personality changes in Patient 3 could have been due to his increased anticonvulsant therapy or to a frontal lobe lesion. As he appeared to improve considerably with reduction of anticonvulsant drugs, no further investigations were done. We therefore consider this a false-positive Ge(Li) scan. Patient 11 had multiple parieto-occipital abscesses confirmed at autopsy. Patient 12 had radiation necrosis of the temporal lobe which was confirmed at operation by biopsy (see Fig. 2).

Negative scans

One-hundred-and-forty-five NaI(Tl) scans were negative while 134 Ge(Li) scans were negative and in 133 cases both were reported as negative.

Summary

There was agreement of the two types of scans in 152 out of 165 cases, *i.e.* 92 per cent. The Ge(Li) scans were definitely superior in 11 cases (6·6 per cent) with one other probable false positive. Expressed in another way, the detection rate on the NaI(Tl) scan was 12 per cent while on the Ge(Li) scan it was 18 per cent.

DISCUSSION

The experience gained with a semiconductor scanner in a clinical trial over some three years has shown that no practical difficulties exist in using

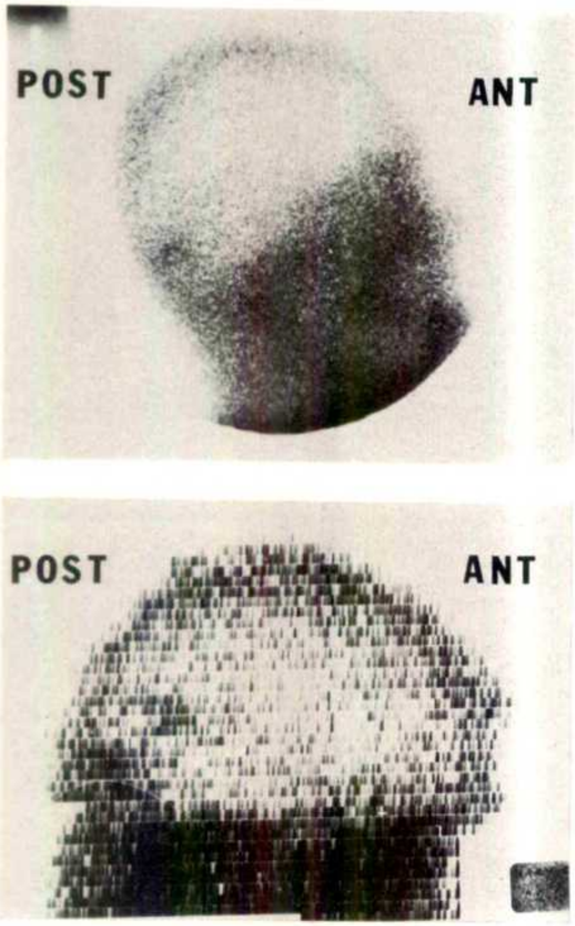

FIG. 2.

There is a well defined "lesion" in the right occipital region on the Ge(Li) scan (lower) which is not visible on the corresponding gamma-camera view.

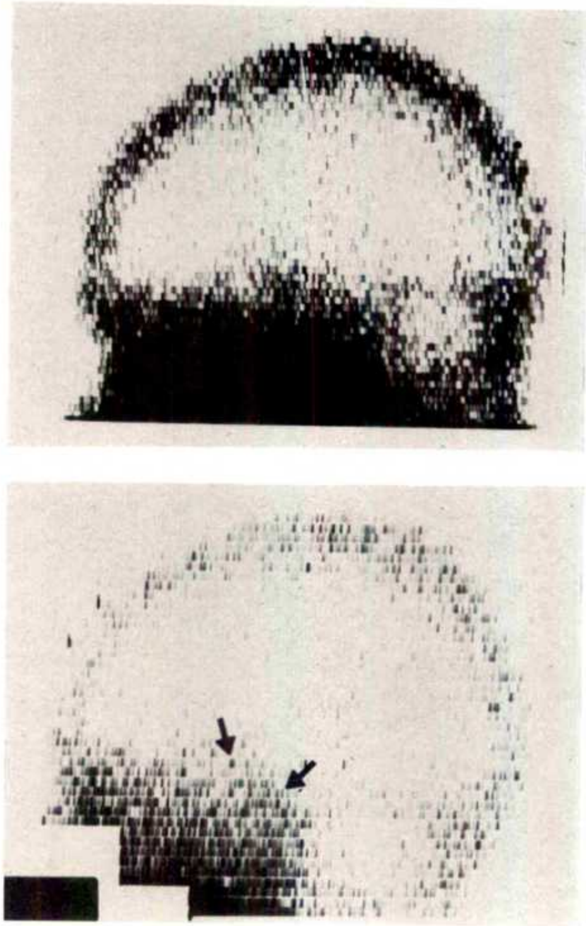

FIG. 3.

The Ge(Li) scan (lower) shows a "lesion" in the left temporal region. The "lesion" is not identified on the NaI(Tl) scan (upper) and appears to be merged with the activity at the skull base.

Ge(Li) detectors in routine scanning. The main limitation found was the low sensitivity of the prototype detectors used. Among the patients investigated, several cases were found in which the semiconductor scanner provided improved diagnostic information which was confirmed in four cases where follow-up information was available.

Of the remaining eight patients whose scan was positive only on the Ge(Li) detector it will be noted that in seven the scan was appropriate, that is, correctly sited for the patient's clinical state. This evidence, although circumstantial, suggests that such findings are significant.

The NaI(Tl) and Ge(Li) scans were performed at approximately one and two hours respectively, except the last 46 sets of scans in the series for which the sequence of examination was randomized. Previous workers (Gates *et al.*, 1971; Tauxe and Thorsen, 1969) have found some evidence that delaying technetium scans up to four hours may give increased information, and in the randomized studies each of the positive Ge(Li) scans followed the NaI(Tl) scan but no case was found for which a late NaI(Tl) scan showed extra appropriate information missing on the earlier Ge(Li) scan.

Allowing for the time difference and for the different collimators used, the results indicate that an improvement in scan quality may be obtained by using a Ge(Li) scanner and it has proved possible to identify a small number of abnormal scans which would otherwise have been missed. This is particularly so when lesions lie in the basal regions, or are of such a size or activity that they can be easily obscured by radiation scattered from adjacent areas. It could be argued that there is no necessity for the expense and complexity of a Ge(Li) detector: a smaller window could be used with NaI to achieve the same result. While this is true, and the present work is in the nature of a feasibility study, Ge(Li) detectors are capable of considerable further development, whereas the NaI detector has been developed to maximum sensitivity already.

CONCLUSIONS

Further investigation is required to compare a larger, more sensitive Ge(Li) detector scanner with a current generation gamma-camera. Both instruments could be expected to give significantly better results than those obtained in the last two to three years. Conclusive demonstration of small changes in performance is difficult in the clinical situation and factors such as the convenience of multiple view studies on gamma cameras cannot be ignored.

ACKNOWLEDGMENT

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Book review

Radiologic Science for Technologists. By Stewart C. Bushong, pp. 343, illus., 1975 (C. V. Mosby Co., distributed by Henry Kimpton), £7·45.

Radiologic Science is based on lectures given to American radiological technology students, and has therefore already been tested and tried; except in one or two instances, it is not found wanting.

It comprises 17 chapters, ranging from the basic concepts of radiation and atomic structure, through the physics of X-ray production and interaction, and the design of main and accessory X-ray equipment, then on to the photographic aspects of intensifying screen and film. The final chapters cover radiobiology and aspects of radiation protection—the latter topic also being mentioned earlier in the text. It is thus seen to be a comprehensive volume.

The chapters are well set out; the script is clear and succinct, and plentifully illustrated—often light-heartedly, though never at the expense of clarity and accuracy.

All mathematical formulae are clearly outlined, and problems using these are deduced in the text. At the end of each chapter, there are up to ten review questions, and one is pleased to note that the answers to the numerical ones are found at the back of the book. These aspects make the book useful for self-study, and students can ensure that they have grasped the material in each chapter before moving on to the next.

There are some points about personnel monitoring with which I would take issue. The British Code of Practice, and the International Commission on Radiological Protection do not advocate the wearing of a single monitoring device on the collar outside a lead rubber apron. It is, after all, the gonads and spinal bone marrow that are most at risk from radiation, so it is the doses to these areas that need to be checked, rather than the dose on the outside of a protective coat. Much of the paragraph "Where to wear a personnel monitor" (page 320) is debatable, and requires editing before a student absorbs it.

A smaller point is this. Can thermal conductivities of 0·45 units (W) and 0·92 units (Cu) really be considered "nearly equal"?

However, apart from the strangely awry remarks on monitoring, the book is essentially sound and readable and will be an asset to a student radiographer or trainee radiologist. It would be true to say that Mr. Bushong has succeeded in his aim of making "Physics fun"—more so than other authors I have encountered.

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Scanning electron microscopy of mouse intestinal mucosa after cobalt 60 and D-T neutron irradiation

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ABSTRACT

The stem-cell population of the intestinal crypt is an important model system in experimental radiobiology. Standardized techniques have been developed to allow quantitation of the response of crypt cells to radiation injury following doses of 0–2 krad of D-T neutrons or ^{60}Co γ rays. These techniques rely on the identification of regenerating crypt cells three-and-a-half days after irradiation. The results are expressed as the number of regenerating crypts per circumference of small intestine, as determined by conventional histological examination; the more profound the injury, the smaller the crypt count. The practical relevance of crypt-counting techniques to clinical radiotherapy is limited by their relative insensitivity; the dose levels commonly used in fractionated radiotherapy produce no detectable response.

Scanning electron microscopy of the mucosal surface provides a more sensitive measure of radiation injury. The earliest detectable changes occur at the level of 300 rad of γ radiation, well below the threshold of the crypt-counting technique. At around 1,000 rad, where the first drop in crypt counts occurs, there are well-marked morphological changes which become more severe with increasing dose levels. Some differences have been observed between the morphological effects of γ and neutron irradiation at points of radiobiological equivalence in terms of crypt counts (using an RBE value of about 2).

The changes observed may reflect more than the disruption of epithelial cell kinetics. Mucosal morphology is the total expression of many different biological parameters of which the regenerative ability of the crypt cells is only one. The surface microanatomy of the gut may be the most sensitive indicator of radiation injury which is conveniently available for study.

The quantitation of the response of intestinal epithelial cells to irradiation has been made possible by the development of methods for the assay of intestinal crypt survival (Withers and Elkind, 1970; Withers *et al.*, 1970; Hagemann *et al.*, 1970). The disadvantage of such crypt-counting techniques lies in their inability to measure damage at lower dose levels in the range more commonly used in fractionated radiotherapy. A quantifiable effect is only observed after single doses of γ or X-irradiation in the range 1–2 krad, although a temporary perturbation of the kinetics of the cell population can be observed after lower doses (Lesher, 1967). This effect of radiation on the cell kinetics of the proliferative compartment is expressed as failure to maintain epithelial integrity. Since stem-cell injury caused by lower single doses is not expressed on the crypt count scale, it is apparent that a more sensitive technique is required for the study of this dose range.

The scanning electron microscope is now a well-established tool for the study of intestinal surface morphology (Jacques *et al.*, 1965; Carr and Toner, 1968; Marsh *et al.*, 1968; Toner and Carr, 1969). The qualitative changes produced by radiation have been described by Carr and Toner (1972) and Anderson and Withers (1973). The present study describes an attempt to bring together the qualitative and the quantitative approach in order to build up a more complete picture of the acute intestinal response to irradiation. The effects of ^{60}Co γ rays and D-T neutrons on the mouse gut have been studied over the dose range 0–2 krad, using both scanning microscopy and a crypt-counting method based on that of Withers and Elkind (1970). To eliminate possible sources of error, the effects on control and irradiated intestine of different degrees of distension by fixative have also been investigated. (These data have been reported briefly: Carr *et al.*, 1975.)

MATERIAL AND METHODS

Adult C_3H mice 10–15 weeks old were exposed to single doses of ^{60}Co γ rays and D-T neutrons. All exposures, both neutron and γ irradiations, were to the whole body. Tissues were prepared for light and electron microscopy.

Irradiation procedures and dosimetry

The ^{60}Co γ-ray exposures were carried out on an Orbitron therapy unit. A Perspex jig containing four animals was positioned in its broadest field such that the centre line of each mouse was 40 cm from the source; the dose-rates to the tissue under these conditions, approximately 180 rad minute^{-1} over the period of the experiments, were measured using a tissue-equivalent (TE) chamber designed for the neutron experiments, which was placed at the centre of a Perspex mouse phantom in the jig. The TE chamber was in turn calibrated against an NPL secondary standard Farmer-Baldwin ionization chamber under standard conditions.

The neutron source used was a P-tube sealed D-T generator supplied by Elliot Bros. (London) Ltd., which provides primary neutrons of mean energy 14·7 MeV in the direction of the ion beam incident on the neutron producing target. During the irradiations, two animals were placed in Perspex tubes situated with the centre axes parallel to and 8 cm from the plane of the neutron source. The hind 4 cm of the two animals were centralized over the source and during irradiation the tubes were slowly rotated to ensure uniformity of exposure.

Neutron spectrum measurements were available for similar irradiation conditions (Lawson *et al.*, 1972) and the doses received by the animals were estimated to comprise 76 per cent from primary neutrons of 14·7 MeV, 19 per cent from scattered neutrons of mean energies 1·1 MeV, and 5 per cent from γ rays. The actual doses given to each pair of animals were controlled by two monitor fission chambers which were regularly calibrated against the TE ionization chamber placed in a mouse phantom in the irradiation jig. Dose-rates to tissue for the neutron exposures were in the range 5–12 rad minute^{-1}.

Tissue preparation and microscopy

The mice were killed three-and-a-half days after irradiation by cervical dislocation and two segments of the proximal small intestine were removed. One segment was embedded in paraffin wax, sectioned (5 μ), and stained with haematoxylin and eosin. The number of surviving crypts per circumference was then counted. The second segment was flushed and then inflated gently with fixative, the ends tied off and the segment immersed in fixative (Carr and Toner, 1972).

In addition to the usual controls, tests were made of the effects of different degrees of distension of the gut by fixative. Under-inflated and over-inflated segments were compared in both normal and irradiated animals. The fixatives used in the experiments were either 10 per cent formol saline or 2 per cent phosphate-buffered glutaradehyde at pH 7·4. Following adequate fixation, the inflated gut was opened longitudinally along the line of the mesentery and washed out with buffer solution. Suitable portions of tissue were post-fixed in 1 per cent Osmium tetroxide for one hour and then washed in water, after which the tissue was pinned out on cork and air-dried. Trimmed samples were mounted on specimen carriers with adhesive solution and vacuum coated with gold-palladium. The tissues were examined with an S600 scanning electron microscope (Cambridge Scientific Instrument Company) used in the emissive mode at accelerating voltages of from 1·5 kV to 25 kV. Recording was done with 35 mm FP4 film or 70 mm FP4 film.

Results

Crypt regeneration after irradiation

Figure 1 shows dose-response curves following ^{60}Co and D-T neutron irradiation. Both curves have similar final slopes, with D_0 values of 180 and 150 rad respectively. (For the purpose of this comparative study enumeration of regenerating crypts provides sufficient data without calculation of the number of stem cells.) Using this system it is possible to compare the effects of the two different radiations at the same quantitative level of biological damage, expressed as the mean number of surviving crypts per circumference of intestine. The RBE for D-T neutrons compared to γ-radiation falls slightly with

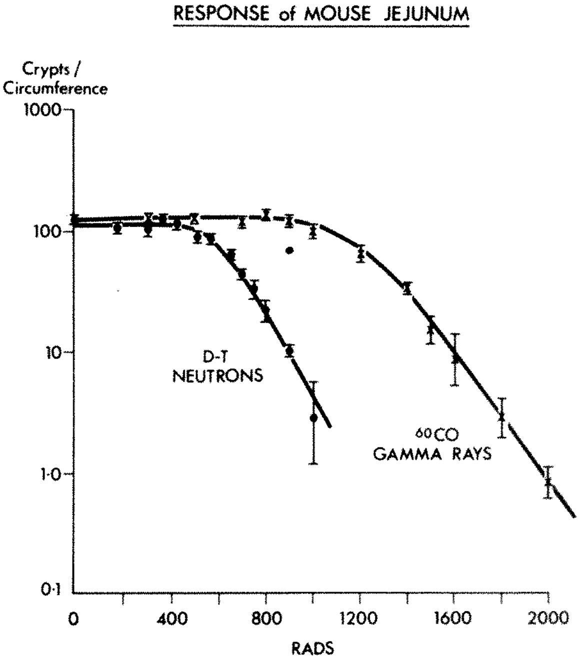

Fig. 1.

Dose-response curves of mouse jejunal crypt survival after single doses of D-T neutron and ^{60}Co γ irradiation. (The points show the means and standard errors of the means of data pooled from at least four experiments.)

increasing dose from 2·1 to 1·8, expressed at several points along the crypt survival co-ordinate.

Also clearly demonstrated are the large 'shoulders' to the two curves which are attributable to cell multiplicity in the crypts and accumulation of sublethal damage by the crypt cells. This limits the discrimination of effect to relatively high dose levels. For γ irradiation the first significant deviation from this shoulder occurs at around 1,000 rad, whereas in the neutron series the corresponding first biological effect is seen at doses around 500 rad.

Scanning electron miscroscope investigation of control specimens

Figure 2A shows a segment of intestine from an unirradiated control animal. Although there is slight variation in the morphology of the villi, over the series as a whole the control animals display structural characteristics in agreement with those described in the literature.

To eliminate possible sources of error, the effects of different degrees of distension of the small intestine by fixative were considered, since a random element was inevitable at this point in the preparation of specimens. It was found that increasing distension of the normal control intestine (Fig. 2B) caused increased separation of the villi with some minor variations in their orientation. Changes in the surface contours of the villi were not produced by distension. Bending or twisting of villi did not occur and the villi were not distorted into conical or leaf patterns. After very high doses of neutron or γ-irradiation (reducing survival to about one crypt per circumference), chosen to maximize tissue damage

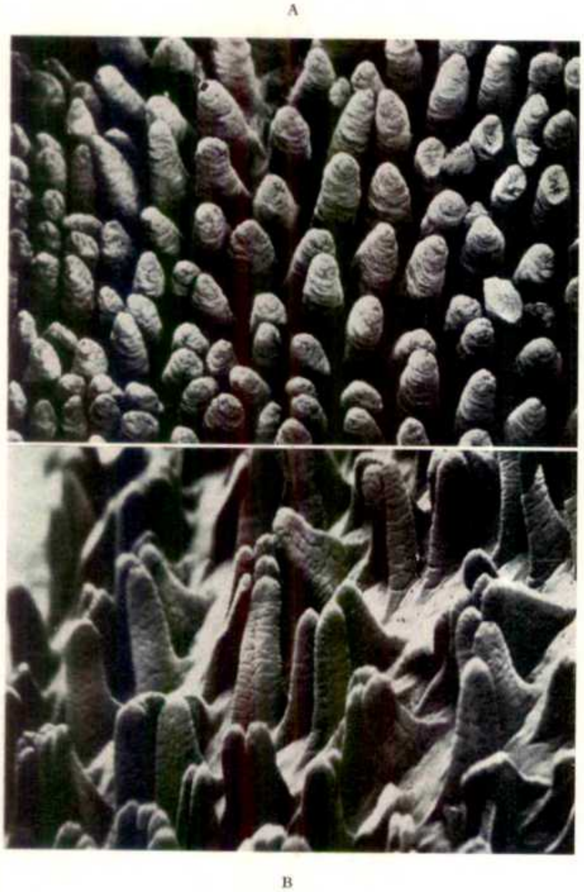

Fig. 2.

Scanning electron micrographs of normal mouse jejunum
(A) after standard distension;
(B) after overdistension.
(×100)

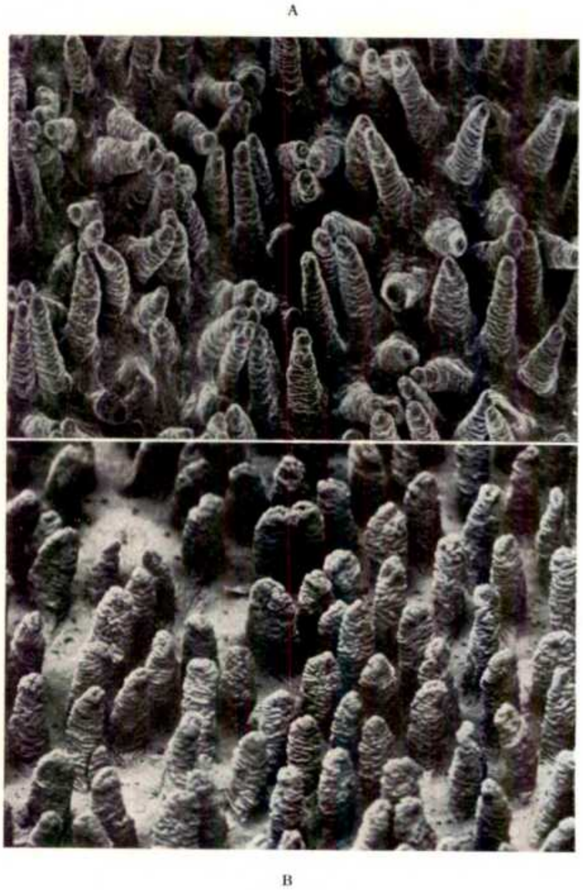

Fig. 3.

Scanning electron micrographs of mouse jejunum $3\frac{1}{2}$ days after
(A) 1,000 rad γ irradiation;
(B) 500 rad neutron irradiation. ×(100)

and hence perhaps to make the specimens more vulnerable to the effects of distension, the following observations were made: in highly distended specimens wider separation of villi were again observed, which made the surface abnormalities produced by the irradiation all the more apparent; the distension did not itself increase the mucosal irradiation damage already present.

'Shoulder' doses

As previously stated, the first depression of crypt count occurs at 1,000 rad for ^{60}Co γ irradiation and 500 rad for D-T neutron irradiation. At these two corresponding points there are clear-cut alterations in the mucosal surface as seen by scanning electron microscopy. Gamma-irradiated specimens (Fig. 3A) retain the slender villi of the control intestine, but their orientation is inconsistent and groups of villi appear to clump together. Individual villi are more often bent or twisted than in control samples; the tips of the villi are often mis-shapen to a greater degree than their more proximal portions; the surface creases of the villus, which form, in the control, an orderly pattern of circumferential grooves, are less consistent in their contours and in their arrangement. Neutron-irradiated specimens (Fig. 3B), showing the same relative biological effect in terms of crypt-counts, also show morphological abnormalities. As in the γ series there is an irregularity in the disposition of the surface markings and a change in their nature; these now appear more as rough corrugations of the villus surface than as the linear creases seen in the controls; in addition, neutron-damaged villi are consistently more conical in profile than controls and γ-irradiated specimens; many of the villi broaden out at the base and take on a flattened tongue or leaf shape, which is a marked departure from control morphology in the mouse. To sum up, well-established qualitative changes accompany the first quantitative evidence of intestinal mucosal damage.

Higher doses

Progressively increased doses of irradiation beyond this initial quantitative threshold produce an exponential fall in the counts of surviving crypts (Fig. 1). The morphological changes seen by scanning microscopy are also progressive. Thus, at dose levels which reduce survival to about ten crypts per circumference, after γ irradiation (Fig. 4A) the villi retain their initial slender contours, although surface irregularity becomes progressively more obvious. Twisted, bent and clumped villi are more numerous and marked distortion of the tip of the villus is often seen at times with concave indentations. After an equivalent dose of neutron irradiation (Fig. 4B) the tendency towards flattened and conical villi persists, while not becoming significantly more marked. The surface contours are strikingly abnormal, the corrugations being no longer largely circumferential but now also vertical. While some specimens show a degree of bending and twisting of villi, this is a less striking feature than in γ-irradiated mucosa. The qualitative mucosal changes therefore, while depending to some extent on the type of radiation, run parallel to the

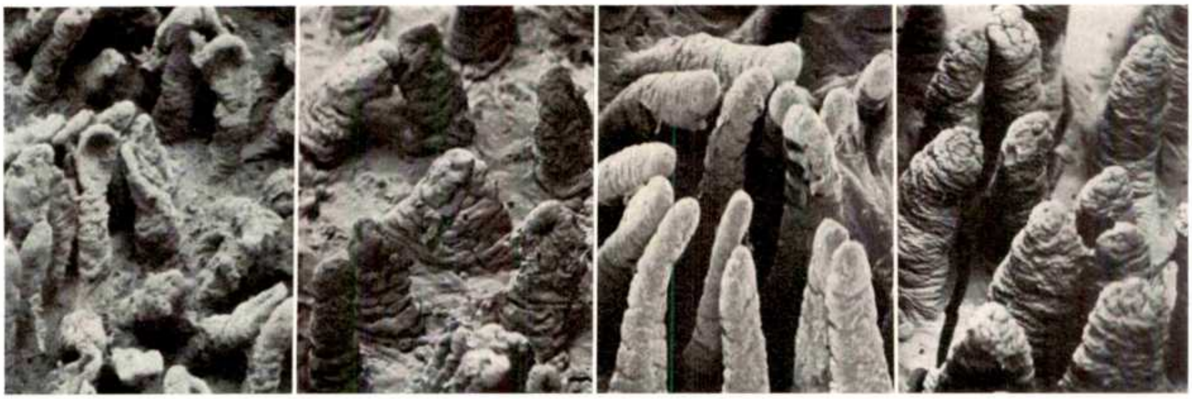

Fig. 4.

Scanning electron micrographs of mouse jejunum 3½ days after
(A) 1,600 rad γ irradiation;
(B) 800 rad neutron irradiation;
(C) 300 rad γ irradiation;
(D) 170 rad neutron irradiation. (×200)

quantitative changes on the exponential portion of the survival curve, becoming increasingly severe with increasing dose.

Low doses

Qualitative results are also found in specimens which lie on the horizontal portion of the survival curve which is below the threshold of discrimination of crypt-counting techniques. In the γ series (Fig. 4C) minor changes in villus orientation are first observed after doses of 300 rad, about one-third of the dose level required to produce a significant depression in the crypt count. Little change is seen in the surface creases of the villi, but slight distortion is present at the tips of some villi. A dose of 170 rad of neutrons (Fig. 4D), which might be expected to have an approximately equivalent biological effect, also produces minor changes, with slight swelling and broadening of villi and a distinct irregularity of surface creases.

DISCUSSION

The results obtained with the regenerating crypt system and presented in Fig. 1 were qualitatively comparable with previously published work (Withers *et al.*, 1970; Broerse *et al.*, 1971) although values for D_0 and RBE were higher. This may be due to the use of different strains of mice and of ^{60}Co γ radiation.

The crypt-counting technique gives standardized, consistent and easily reproducible quantitative data concerning radiation damage to the stem cell population of the intestinal epithelium by higher doses of radiation. It is, however, a relatively insensitive indicator of total mucosal damage. Scanning electron microscopy produces visual results which express this damage in terms of surface changes in the injured mucosa. The results are not at present satisfactorily quantifiable. Qualitative changes such as these are intrinsically difficult to quantitate, although work is now in progress to isolate and measure specific components of the mucosal injury. Preliminary estimates of villus height from stereopairs, using a Hilger Watt stereoscope, confirm, for example, that neutron irradiation produces a decrease. Even without complete quantitation, qualitative results at the lower dose levels commonly used in clinical radiotherapy provide a much more sensitive indicator of mucosal damage than does the crypt-counting technique.

Our results suggest some differences in the qualitative expression of the mucosal damage resulting from the two forms of radiation used in these experiments. In particular, neutron damaged villi are consistently more conical than γ-irradiated specimens. Although the reasons for this remain obscure, we have so far found it possible to discriminate by scanning microscopy between neutron and γ irradiation specimens throughout the range of doses covered in this study. If further research confirms this, it will prove a useful application of the qualitative technique. It would seem that the many biological variables which contribute to intestinal morphology are independently and differently affected by neutron and γ irradiation. Perhaps, for example, at a given level of radiobiological effect as measured by crypt counting, the intense local ionization of the neutron beam produces more pronounced vascular effects than the diffuse ionization of γ irradiation. Mucosal morphology is the total expression of many different biological parameters; the regenerative ability of the crypt epithelium is only one of them.

The need for standardized tissue preparation techniques has been pointed out by Anderson and Withers (1973). The results of our distension experiment confirm the desirability of standardization; it appears likely, however, that the relatively small variations between specimens are unlikely to lead to any serious misinterpretation of the ultrastructural effects of irradiation.

In conclusion, the qualitative technique of scanning electron microscopy provides a more sensitive indicator of mucosal irradiation damage at low dose levels than conventional quantitative techniques. There is also evidence that a study of mucosal morphology may provide a means of discriminating between the effects of different types of radiation at dose levels which are radiobiologically equivalent on certain quantitative scales.

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Book review

Principles of Bone X-ray Diagnosis. By George Simon, 3rd edn., pp. xix + 232, 343 illus., 1973 (London, Butterworths), £9·80.

The author of this book is one of the legendary radiological teachers of our time. Generations of trainees have been held in thrall at his lectures and tutorials and have willingly submitted to an oft-times painful and searching inquisition in the process. In 1956, *Principles of Chest X-Ray Diagnosis* was written which introduced the original concept of grouping diseases together according to their radiological appearance. The great success of this approach was followed by a similar treatment of disorders of the skeleton.

This work is now in its third edition, sufficient testimony of the sustained popularity and esteem in which it continues to be held. An excellent systematic introduction to the radiological diagnosis of musculoskeletal disease is provided. The author concentrates on the basic manifestations of the response of bone to different disease processes, supplemented by pathological and histological evidence where necessary. The radiological illustrations are of the highest order and over 50 fresh examples have been included for this latest edition.

Readers will find chapter headings which deal with the following types of bone change: Alteration in Shape, Position, and Density, Periosteal Shadow and Combination of Shadows. The chapter on "Widespread and Regional Reduction in Bone Density" has been written in collaboration with Dr. J. Y. Woodhouse. There is a short introduction to each chapter to set the subject in perspective.

One might wish that an opportunity could have been taken to amplify these introductory paragraphs even further. The reader could then derive greater insight into the author's analytical approach to decision-making in consequence of his considerable radiological experience. At the same time, it is recognized that this objective is easier to achieve with the spoken word rather than the written one.

Tables of "Normal Biochemical and Haematological Values" have been thoughtfully provided along with some "Hints on X-Ray Technique". One statement in this section does require some amplification however. "If a special X-ray tube with an even smaller focal spot (*i.e.* less than 1 mm) is available, it will be best for peripheral limb radiography." In fact, for practical purposes, there is no visually detectable blurring from geometric unsharpness in the radiograph of a thin subject, *e.g.*, the hand, in contact with the film with the X-ray tube set at 100 cm. Therefore, in that context, selection of the focal spot size is immaterial. Small spot X-ray tubes are of course, most appropriate for those circumstances in which the film and the object are separated, as in magnification work.

George Simon has the enviable ability to get straight to the heart of a matter. The book is infused with practical information, common sense and good radiological practice. Over the years, his work must have graced the teaching libraries in many lands. It is a pleasure to welcome this latest edition and to salute the contribution which he has made to the clinical practice of radiology.

W. M. PARK.

1976, *British Journal of Radiology*, *49*, 630–634

Measurements of neutron spectra at depths in tissue equivalent material for fast neutron beams generated by deuterons on beryllium

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Abstract

The threshold foil technique has been used to investigate the behaviour in tissue of the spectra of neutron beams produced by the bombardment of thick Be targets with 13·0 and 20·5 MeV deuterons. The results indicate a gradual "softening" with depth in tissue of the spectrum generated by 20·5 MeV deuterons which contrasts with a gradual hardening as reported by other authors. This is discussed in terms of the significance of field size and the methods used for data collection and analysis.

There is considerable interest in the use of fast neutron beams for radiotherapy (Catterall, 1974; Catterall and Vonberg, 1974) and diagnostic purposes (Harvey *et al.*, 1975). Studies of the radiobiological effects of such beams have been conducted at various centres (Field, 1969; Broerse *et al.*, 1971). Recently it has been proposed to use the University of Birmingham's 150 cm Nuffield Cyclotron for a study of certain radiobiological aspects of fast neutron beams produced by bombardment of thick beryllium targets with deuterons.

The purpose of this paper is to report the results of measurements of the behaviour in tissue of the spectral shape of two different neutron beams produced from bombardment of a beryllium target with 20·5 MeV and 13·0 MeV deuterons. The measurements were made by the threshold foil technique at closely spaced intervals of axial distance up to a depth of 16 cm in a tissue-equivalent phantom.

Information on the behaviour of spectral shape in tissue is essential, since changes in the spectrum at depth will produce corresponding changes in the radiobiological response and oxygen enhancement ratio. Field and Parnell (1965) have reported a slight hardening over a depth of 30 cm for the heteroenergetic spectrum produced by the M.R.C. cyclotron at the Hammersmith Hospital, London, the effect being most noticeable for smaller field sizes. Hannan *et al.* (1973) have detected a gradual softening along the axis of a 15 MeV monoenergetic neutron beam produced by a D-T generator. Both reports concluded that there was unlikely to be any noticeable change in radiobiological response.

The Threshold Foil Technique

There are several different methods for evaluating neutron spectra from threshold foil measurements (Beckurts and Wurtz, 1964; Field and Parnell, 1965; Lawson *et al.*, 1972). In general the cross-section for activation of a foil may be approximated to that of a step-function; *i.e.* above an effective threshold energy (E_t) the cross-section has a constant value (σ_0); below this energy it is zero. The total number of interactions per second in the target foil is given by:

$$A = n\int_{0}^{E_{\max}} \phi(E)\sigma(E)dE = n\sigma_0\int_{E_t}^{E_{\max}} \phi(E)dE \qquad (1)$$

where n is the total number of target nuclei in the foil, $\phi(E)$ is the variation of the neutron fluence with energy, $\sigma(E)$ is the actual reaction cross-section variation with energy and $E_{\max}$ is the maximum neutron energy. For some reactions, the parameters σ_0 and E_t have been calculated and listed (Beckurts and Wurtz, 1964). By selecting a range of reactions whose effective threshold energies cover the neutron spectral energy range, a histogram of the spectrum can be unfolded with energy bin widths corresponding to the separation of these effective threshold energies. The foils chosen for the measurements reported here are listed in Table I.

TABLE I

Effective thresholds of the reactions

Element	Reaction	Effective threshold energy (MeV)
Indium	$^{115}In(n,\gamma)^{116m}In$	Thermal
	$^{115}In(n,n')^{115m}In$	1·65
Iron	$^{56}Fe(n,p)^{56}Mn$	7·70
Aluminium	$^{27}Al(n,p)^{27}Mg$	5·30
	$^{27}Al(n,\alpha)^{24}Na$	8·15
Nickel	$^{58}Ni(n,2n)^{57}Ni$	14·0
Titanium	$^{46}Ti(n,2n)^{45}Ti$	16·0
Carbon	$^{12}C(n,2n)^{11}C$	20·0

EXPERIMENTAL METHOD

The beryllium target, a collimator and a phantom were located in a tunnel passing through a 180 cm thick wall adjacent to the cyclotron (Fig. 1). This tunnel lay along a horizontal axis, roughly parallel to the deuteron beam pipe, and at a height of about 200 cm above the floor. For the purposes of this work, a collimator of 50 cm length and cross-section matching that of the tunnel was constructed of polyethylene with a central untapered aperture to provide a neutron beam field size of 8 × 5 cm.

The phantom consisted of a Perspex tank filled with a tissue-equivalent fluid. The composition of the tissue-equivalent fluid was 68 per cent H_2O, 22 per cent glycerol, 7·8 per cent urea, 0·8 per cent $K_2S_2O_8$, 1 per cent $CaHPO_4$ and 0·4 per cent NaCl. Foils were positioned reproducibly in this phantom at depths of 0 cm, 1 cm, 2 cm, 4 cm, 6 cm, 8 cm, 12 cm and 15·8 cm, along the beam axis. These foils were 1 cm diameter and less than 250 μm thick except for the carbon foils which were 3 mm thick. In all cases the effect of shadowing was calculated to be less than 0·3 per cent. The first of these positions was against the outer face of the tank at 60 cm from the beryllium target. The positioning of these foils was such that there was 11 cm of tissue-equivalent material above them and 20 cm below them (Fig. 1).

NaI(Tl) detectors (7·5 × 7·5 cm) and a 60 cm^3 Ge(Li) crystal were used to detect the activity induced in the foils. Three NaI(Tl) detectors were employed to minimize cyclotron running time and the Ge(Li) detector was necessary for counting the closely spaced γ rays from the indium foils. γ-emitting sources were used to obtain the relative efficiencies, as a function of energy, for the four detection systems. Absolute efficiencies of the NaI(Tl) detectors were extracted from the literature.

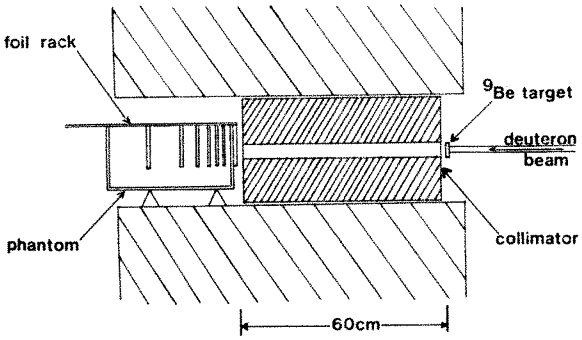

FIG. 1.

A schematic representation (not to scale) of the arrangement used for foil irradiation.

The fast and thermal neutron fluences were measured at the nine positions in the phantom for the neutron beam produced by 20·5 MeV deuterons. A copper foil of thickness 250 mg/cm^2 was then inserted immediately in front of the beryllium target. This thickness had the effect of degrading the deuteron beam energy from 20·5 MeV to 13·0 MeV. It was estimated that this copper foil produced a forward scattered fast neutron yield of about 6 per cent of that produced from the bombardment of the beryllium target with the degraded deuteron energy of 13·0 MeV (Allen *et al.*, 1951). For this lower deuteron energy the fluence measurements at 1 and 12 cm depth were omitted. Because the threshold energies for the reactions in the carbon and titanium foils are either greater than or the same as the maximum neutron spectral energy at this lower deuteron energy, no activity was observed from these foils placed at the 0 cm depth, and they were therefore omitted from the other depths.

The long-term stability of the cyclotron performance was checked by counting the activity induced in an iron foil which had been irradiated at the 0 cm depth position.

RESULTS

The relative efficiencies of the NaI(Tl) crystals were found to lie within a few per cent of each other. Evaluation of the fluence incident on the 0 cm iron foil irradiated each day revealed a variation of less than 5 per cent, statistical errors of counting being less than 0·2 per cent.

Calculations of the neutron spectra were performed with the aid of FORTRAN and BASIC language computer programs, using the activities measured in the foils and normalized to a deuteron target current of 10 μA. On determining the spectrum at 0 cm, for a 20·5 MeV deuteron beam, it was found that the average fluence in the lowest energy bin (1·65–5·30 MeV) was three times the average fluence in the next highest energy bin (5·30–7·70 MeV). This compared most unfavourably with the spectrum of Cohen and Falk (1951). This latter spectrum was obtained in air; however, the extra backscatter of neutrons (from the surface of the phantom) in our results is insufficient to produce the observed difference. Since the spectral unfolding process starts with the foil having the highest effective threshold energy, then from consideration of equation (1), it was concluded that too high a value of cross-section had been used for each foil above their respective threshold energy bins, the values of cross-sections being taken from Beckurts and Wurtz (1964). The spectrum at this depth was recomputed using the same energy thresholds as before, but using actual empirical cross-sections averaged for each energy bin (Aliev *et al.*, 1970, O'Connell, 1971; Brill *et al.*, 1961; Alley *et al.*, 1968). With these revised values of cross-section, it was found that negative values of fluence were unfolded for the narrow energy bins defined by the effective threshold energies of the reactions $Al^{27}(n,p)Mg^{27}$, $Fe^{56},(n,p)Mn^{56}$, and $Al^{27}(n,\alpha)Na^{24}$ for both deuteron energies at all depths.

This is a problem associated with any "unfolding" technique of data analysis and is a result of uncertainties in supposedly known parameters (*e.g.* cross-section) as well as the statistical nature of the data. To overcome this problem and to produce spectral histograms as regular as possible in bin width, the data obtained from the aluminium foils were omitted. Table II gives the values of cross-section used for each energy bin for the remaining foils. The resultant neutron spectra are comparable with the "in air" measurements of Cohen and Falk.

The spectral histograms at four depths, for both deuteron beam energies, are given in Fig. 2. These spectra are discontinuous below 1·65 MeV due to lack of a foil with an effective threshold energy below this value; the significance of this is discussed later.

The thermal fluence was calculated directly from the activity induced by the thermal capture reaction in indium, and the variation with depth is given in Fig. 3 for the two deuteron beam energies.

CONCLUSIONS AND DISCUSSION

For the conditions of work and method of analysis reported here, certain conclusions were drawn about the threshold foil techniques:

(1) Step-function approximations to reaction cross-sections are of limited use in the evaluation of a continuous neutron spectrum. A more representative result is obtained by averaging the actual cross-section variation over each energy bin of the neutron spectrum.

(2) There is a limit to the useful minimum separation of the effective threshold energies. This limit is governed by the rate of increase of the reaction cross-sections in their respective threshold energy bins—the steeper the rise, the better the discrimination; and also by the accuracy to which the cross-sections may be averaged within the energy bins and by the size of the energy bin over which the averages were taken.

TABLE II

VALUES OF CROSS-SECTION (MBARNS) USED IN EACH ENERGY BIN

Reaction	Energy bin limits (MeV)				
	1·65–7·7	7·7–14·0	14·0–16·0	16·0–20·0	20·0–25·0
$^{12}C(n,2n)^{11}C$	—	—	—	—	3·5
$^{46}Ti(n,2n)^{45}Ti$	—	—	—	200	200
$^{58}Ni(n,2n)^{57}Ni$	—	—	45	65	50
$^{56}Fe(n,p)^{56}Mn$	—	75	100	68	40
$^{115}In(n,n')^{115m}In$	300	200	200	200	200

Consideration of these points suggests that the validity of making a comparison between these results and ones obtained from step-function approximated cross-sections with different threshold energy criteria may be doubtful. Since the cross-sections used here more closely follow the actual cross-section variation with energy, and also because the criterion for determining the effective threshold energies of the reactions was not based on a simple fraction of the maximum cross-section, it was considered that this approach should lead to more representative spectra.

The variation with depth of the spectral shape above 1·65 MeV for the 20·5 MeV deuteron beam appeared to indicate a very gradual softening, with a calculated mean energy decreasing from 9·4 MeV to 8·8 MeV through 16 cm of tissue. If the fast neutron spectrum did soften slightly with depth, then the missing flux information below 1·65 MeV is important, not only because of the rapidly varying and large values of RBE in this energy range, but also because the penetration would be increased. Although without a measure of the flux below 1·65 MeV no definite statement can be made, there was sufficient indication of an opposite effect to the hardening of spectral shape (neutron energy greater than 2·7 MeV) with depth, as found by Field and Parnell (1965) to warrant a search for possible explanations:

(1) As stated before, the spectral shape was found to be sensitive to the use of cross-section approximations, and more detailed values of cross-section have been used in the present work. This should be considered in the context of Field and Parnell's method which was only able to resolve a significant spectral change over depths of 30 cm.

(2) It is possible that the effect of field size on spectral shape in tissue may be significant. Two processes contribute to the change in the fluence in an energy bin as the depth of tissue is increased. Elastic collisions will cause the neutrons in this bin to be scattered away from the beam axis and also out of the energy range of this bin to lower energy values; similarly scattered

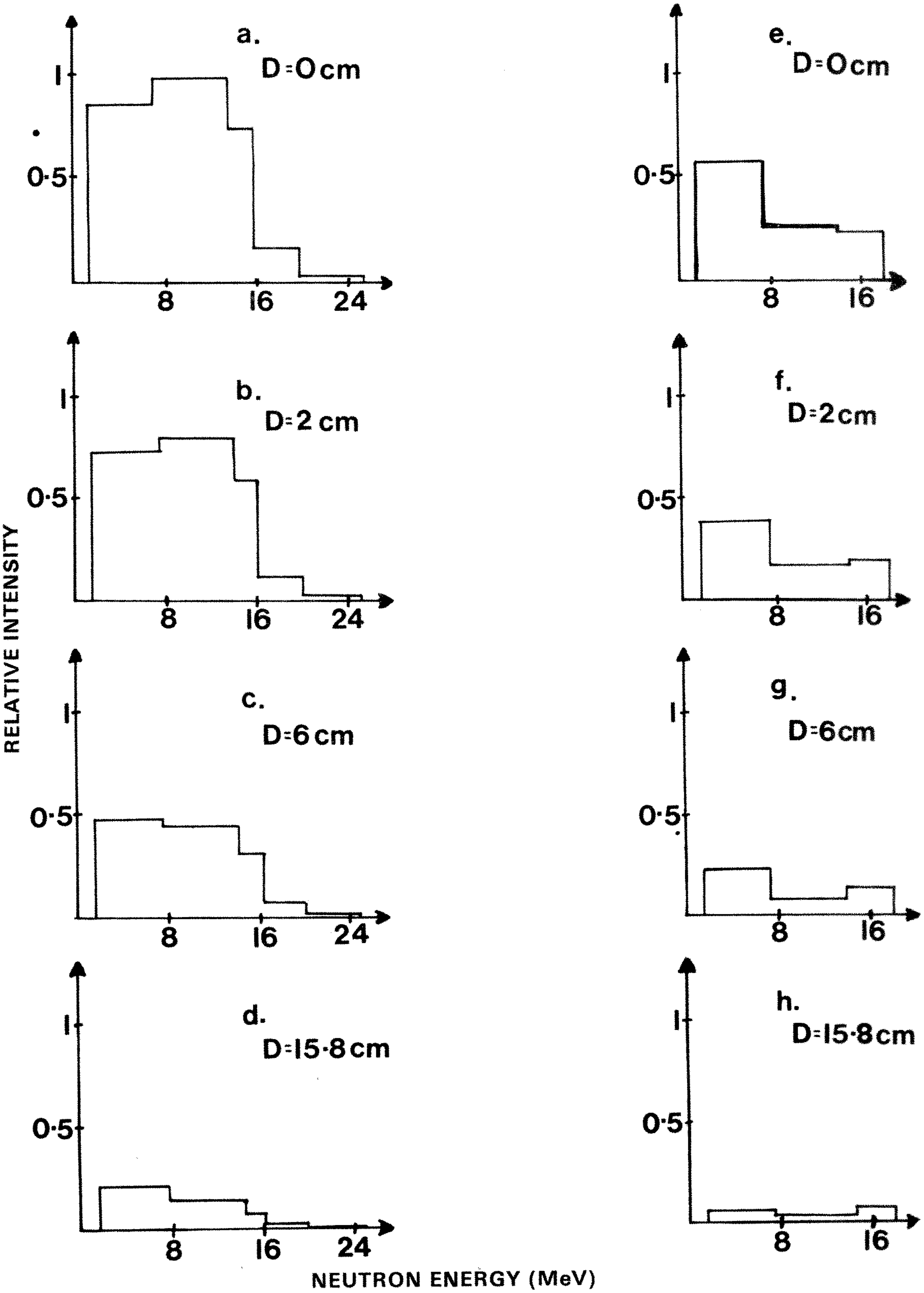

Fig. 2.

Representative histograms of neutron spectra ($E_n > 1{\cdot}65$ MeV) as a function of depth for (a)–(d) 20·5 MeV deuteron energy and (e)–(h) 13·0 MeV deuteron energy.

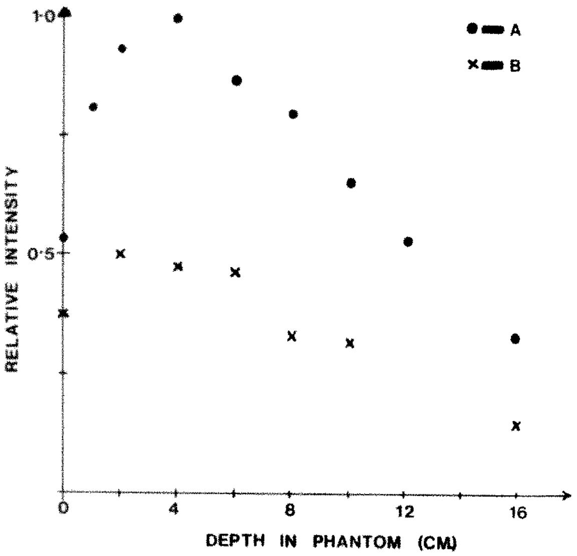

Fig. 3.

Variation of thermal neutron flux with depth in tissue for a neutron beam produced by (A) 20·5 MeV and (B) 13·0 MeV deuterons on a thick Be target.

neutrons from higher energy bins will be scattered into the beam axis and lie within the energy range of the bin in question. These two effects act in opposite directions on the overall spectral shape. The elastic scattering cross-section increases with decrease in neutron energy. However, as the field size is increased more scattered neutrons will be present to increase the second of the two effects described above. Therefore, logically, it might be reasonable to expect an increase in beam softening with depths as the field size is increased; and as the field size is decreased a value must be reached where spectrum hardens with depth due to the first of the above two effects starting to predominate.

This conclusion is compatible with Field and Parnell's results since their slight effect of beam hardening was most noticeable for their smaller field size of 16 cm^2. It is stressed that this possible influence of field size can only be resolved by further experimental work. It is, however, possible that, as suggested earlier, the discrepancy can be explained by the missing spectral information. ($E_n < 1·65$ MeV in our data and $E_n < 2·7$ MeV in the data of Field and Parnell.) Indeed, in our data for an incident deuteron energy of 13·0 MeV we consider this problem does not permit a statement as to "hardening" or "softening" of the spectrum with depth. If an increase in depth and field size was found to cause an increase in spectral softening sufficient to produce a change in biological response, then a brief mention of the radiobiological consequences is relevant. The response of an organ to fast neutron beams can be assessed by the study of the same organ in laboratory animals. In the human case, the organ will be at a greater depth in tissue and a larger field size will be required. Both these factors could combine to change the radiobiological response of the neutron beam at the organ of concern, as compared with the response found from an animal study.

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Grey-scale ultrasonic imaging of the kidney

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ABSTRACT

The ultrasonic appearances of the kidney in images which contain grey shades corresponding to the detected echo-pulse heights have been examined. These "greyscale" images were obtained using a standard Nuclear Enterprises Diasonograph 4102B and a Varian 620/L digital computer interfaced to this Diasonograph. The computer was used to analyse and display the ultrasonograms with 16 grey shades. Both kidneys of 36 subjects were examined and compared with IVU findings. This group included patients with normal kidneys, polycystic kidneys, hydronephrosis, glomerulonephritis and neoplastic tumours. It was found possible to make sharp, grey-shaded ultrasonograms which were very useful to the diagnostician. In particular, the grey shade of the renal parenchyma was used as a standard to compare other grey-shaded structures. Also the grey shading was useful in defining the renal pelvis in transverse scans and the renal poles in axial scan.

Ultrasonic-imaging techniques are used widely in clinical diagnosis. Such techniques produce images which contain details of soft-tissue structures, since they involve the detection of ultrasonic energy which is reflected at discontinuities in soft tissues. In this way a cross-sectional picture of the scanned anatomy is produced. Consequently, ultrasonic images provide information which is complementary to that obtained from X-ray images. In some cases, ultrasonograms provide diagnostic information which is not available otherwise, by a technique which is both non-invasive and non-traumatic.

Ultrasonic-imaging techniques have been applied to renal investigations. The ultrasonic appearances of the normal kidney have been documented (Barnett and Morley, 1971; Mountford *et al.*, 1971), and the appearances encountered in cases of polycystic kidney disease, renal cysts, renal tumours, pyelonephritis, glomerulonephritis, renal calculi, hydronephrosis and perinephric abscess have been described (Barnett and Morley, 1971; Mountford *et al.*, 1971; Holm, 1971).

Recently, ultrasonic-scanning techniques have been advanced by improvements in greyscale ultrasonic images, in which the amplitudes of the low-level echoes which arise from the internal structures of soft tissues are represented by grey shades in the image (Kossoff *et al.*, 1974; Taylor *et al.*, 1973). The inclusion of pulse height information in ultrasonograms by means of grey shading provides a means of differentiating between one tissue type and another and between one disease process and another.

Conventional ultrasonic imaging techniques give rise to artefacts which the scanning device is unable to recognize and allow for (Robinson *et al.*, 1966; Shimmins *et al.*, in preparation). These include multiple reflections of the beam which introduce spurious echoes into the image; effects of signal processing which result in distortion of echo heights and shapes; and uneven scanning of the area of interest which results in non-uniformity of response in the image. In order to overcome some of the problems of processing and displaying ultrasonic pulse-echo information, a small digital computer has been used to preserve the information inherent in the echoes detected from the body. The pulses are processed by the digital computer to sharpen and resolve the echoes, to remove multiple reflection artefacts, and to preserve and display pulse height information, in order to provide high resolution images containing reliable information of diagnostic value. The images produced are life size and are composed of a matrix of 1 × 1 mm cells. Hard copies of the images, which contain 16 grey shades, are produced by an electrostatic plotter. The maximum pulse height detected in any matrix cell is retained in the image, hence removing any non-uniformity of scanning.

The purpose of this paper is to document our initial experience of applying both conventional and digitized grey-scale ultrasonography to a series of examinations of the kidneys.

METHODS AND MATERIALS

The ultrasonic scanning system used in this study is a Diasonograph model 4102B (Nuclear Enterprises Ltd., Edinburgh) which has a Tektronix 611 oscilloscope display with an 8×6 in. screen. The ultrasonic scans of the kidneys are carried out using a 2·5 MHz transducer at a pulse repetition rate of 600 second^{-1}. Grey-scale images are formed at half life-size scale from the screen of the 611 oscilloscope used in short persistence mode and are characterized by their sharpness which is due to the fine spot size. Routine ultrasonic scans of the kidney are made with the transmitter attenuation set to 4 dB and the initial attenuation of the receiver amplifier set to 40 dB. The swept gain function is used with a delay of 20 mm and a slope of 3 dB cm^{-1}. Maximum dynamic range is used throughout.

The Diasonograph is connected to a digital computer (Varian 620/L) and digitized ultrasonic images are produced. The computer has 12 k 16-bit words of core store, a disc memory unit, a magnetic tape unit and an electrostatic printer/plotter (Statos). The computer interface used to connect the Diasonograph to the computer is a development of the interface described previously (Kay *et al.*, 1974), and digitizes the pulse-height information to 16 levels with a sampling width of 1 mm along the A-scan. The efficiency of data collection by the computer has been improved by the use of a storage buffer in the interface (Shimmins *et al.*, in preparation). The digitized images are life size, contain 16 grey shades, and are composed of a matrix of 1×1 mm cells. The grey shades in the digitized images are arranged in a logarithmic manner to represent the smallest echoes which are detectable above receiver noise, and cover a dynamic range of 25 dB. The remaining higher-level echoes are displayed at maximum intensity. Digitized ultrasonic images are acquired by the computer concurrently with the scanning performed for the production of conventional Polaroid grey-scale images taken with the Tektronix 611 oscilloscope. Consequently digitized images may be compared directly with their conventional Polaroid equivalent.

TABLE I

Clinical material

Group	Intravenous Urography findings	Number of patients
A	Normal appearance	18
B	Duplication	1
C	Space-occupying lesion	6
D	Hydronephrosis	8
E	Glomerulonephritis (no IVU)	1
F	Polycystic renal disease	2
Total		36

Clinical Material

Both kidneys of 36 patients and of four asymptomatic volunteers were scanned. Each patient had been referred to the Department of Radiology for routine intravenous urography (IVU). The patients were examined by ultrasound at the same time as their attendance for IVU. The IVU findings of the 36 patients are summarized in Table I.

Opaque surface markers were applied to the patient's back so that, allowing for magnification, the surface markings of each kidney could be obtained from the radiograph. A correction of 1·5 cm was made to compensate for the caudad renal movement when the patient changed from supine (IVU) to prone for ultrasonic scanning. This was the average renal shift in five patients who had one renal area IVU film taken prone instead of supine. Compound sector B-scans of each kidney were taken while the patient suspended respiration. The scans were done in full expiration so that the renal positions were comparable in both IVU and ultrasound examinations. The surface markings made it possible to scan in vertical planes containing the longest axis of each kidney; and in transverse planes containing the hilar structures of each kidney and 2 cm above and below the mid-hilar plane (see Fig. 1).

In order to study the effect of respiration on the quality of the images produced, two patients were examined in suspended breathing, in shallow respiration and during deep breathing.

Results

In patients with normal IVU findings, and in the asymptomatic volunteers, the longitudinal scans

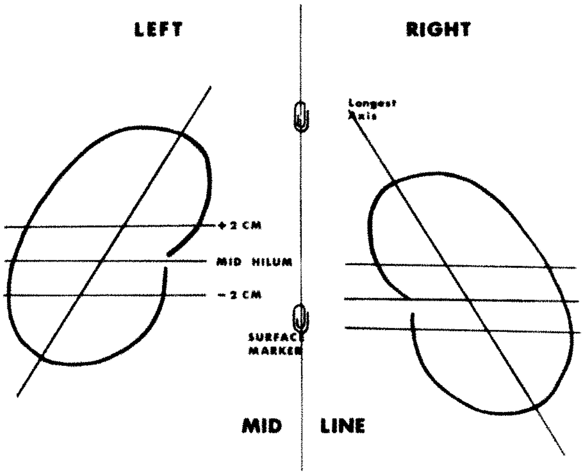


Fig. 1.

Diagram of renal surface markings.

(Fig. 2) through the longest axes of each kidney show a well defined outline which we have termed the "capsule". The "capsule" is less well defined at each pole because of the difficulty in aligning the axis of transducer normal to the capsule at each pole. However, the grey scaling in the image allows the position of the capsule at the poles of the kidney to be determined. A recognizable pattern of low amplitude echoes occupies most of the renal substance, making it possible to distinguish between the renal parenchyma, the collecting system and the perirenal tissues. A characteristic pattern of large amplitude echoes, represented by a wide range of grey shades, form an irregular, elongated, discrete clump in the centre of the kidney. These echoes are considered to represent the major and minor calyces and the renal pelvis, which constitute the major part of the collecting system. Longitudinal sections show recognizable calyceal structure, and individual calyces can be identified. A linear structure can be seen extending downwards in relation to the posterior aspect of the lower pole of the kidney. This structure is considered to represent the ureter.

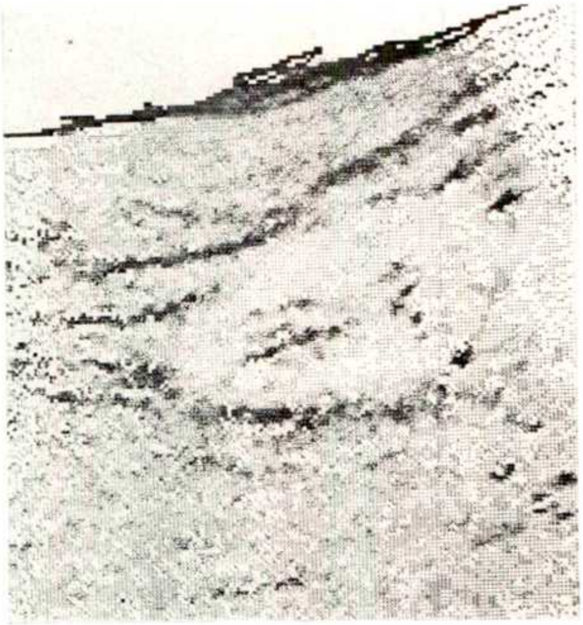


FIG. 2.
Longitudinal scan of normal kidney.

The transverse scans of the normal kidney are characterized by a circular renal outline occupying a paravertebral position (Fig. 3). As in the longitudinal scans, low-amplitude echoes are seen occupying the renal parenchyma. A discrete clump of large amplitude echoes representing the collecting system occupies the antero-medial quadrant of the kidney section in the mid-hilar scan. This clump of echoes moves to occupy a central position in the kidney as each pole is approached. An area with few low-level echoes is seen within the collecting system which is considered to represent the urine filled renal pelvis, and a clear profile of the renal pelvis is seen (Fig. 4).

The images of the kidney with a duplicated collecting system differed from the images of normal kidneys in several respects. The kidney was seen to be considerably elongated, and two separate clumps of echoes were seen centred in the renal substance. These were considered to represent the separate moieties of the collecting system. The appearance of the low-level parenchymal echoes was normal.

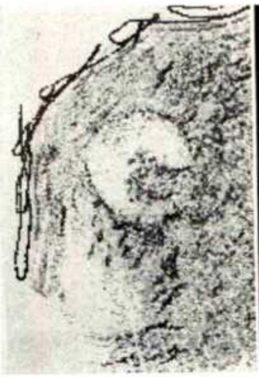
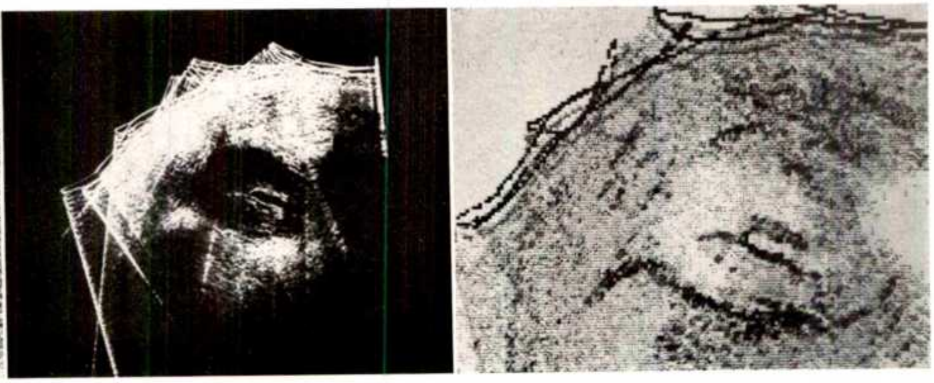


FIG. 3.



A FIG. 4. B

FIG. 3. Transverse scan of normal kidney, at mid-hilar level.

FIG. 4. Transverse scan of normal kidney demonstrating the renal pelvis. (A) Polaroid. (B) Statos print.

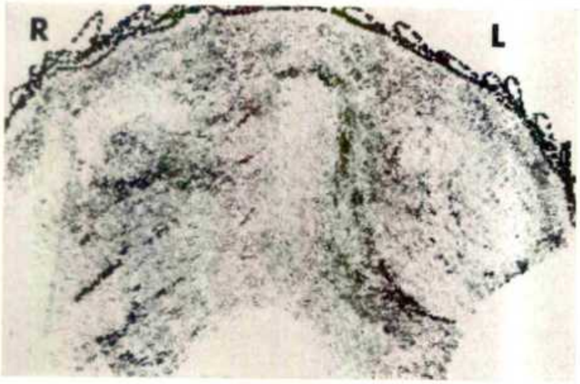
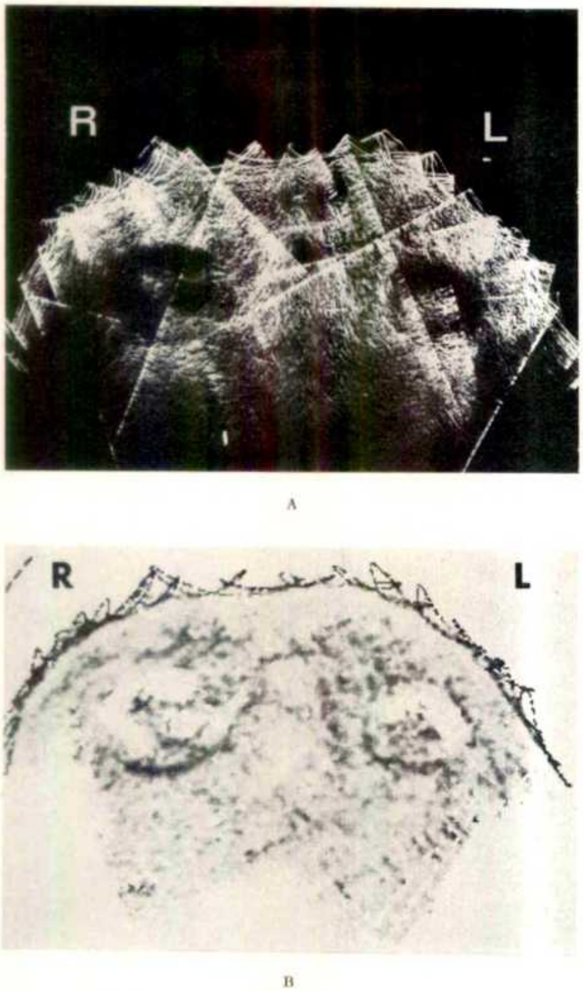


FIG. 5.

Transverse scan showing a large tumour associated with the left kidney and a normal right kidney.



A

B

FIG. 6.

Transverse scan showing a hydronephrotic right kidney and a normal left kidney. (A) Polaroid. (B) Statos print.

Using the grey shades in the image, we were able to demonstrate renal space occupying lesions. In the single example of a large benign renal cyst, the wall of the cyst and the transonic nature of its fluid content were seen. The five remaining renal masses were shown histologically to be malignant. The outlines of these tumours, the relationship of the tumour masses to normal kidney structure, and a bizarre pattern of internal echoes of widely different amplitudes were shown using the grey-scale techniques (Fig. 5).

In the patients with hydronephrosis, the hydronephrotic kidneys were found to show a significant generalized enlargement relative to the normal kidney (Fig. 6). An enlarged transonic area within the collecting system was seen, which represents the dilated renal pelvis. The clump of echoes relating to the collecting system was seen to be fragmented and scattered within the parenchyma. In one case where a renal stone was lodged in the ureter fairly close to the renal pelvis, the stone itself was imaged.

In the single patient with acute renal failure, a clinical diagnosis of progressive glomerulonephritis was made. Because of the patient's severe uraemia (blood urea of 400 mg per cent) no IVU was performed. Confirmation of the diagnosis was not possible since the patient died before renal biopsy could

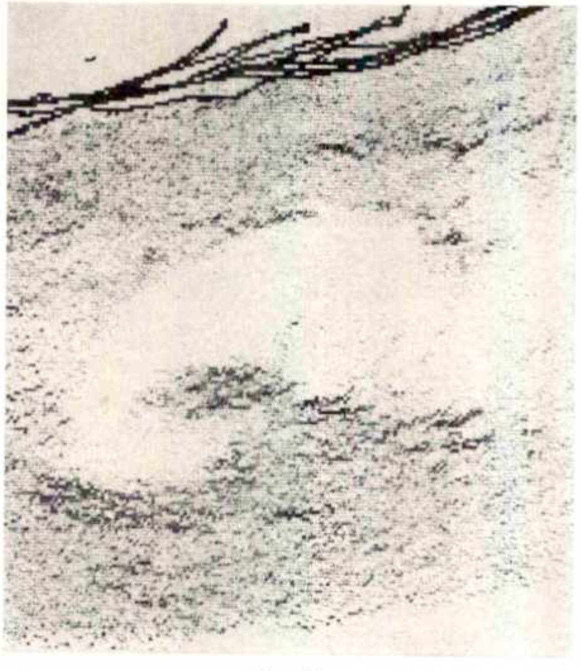
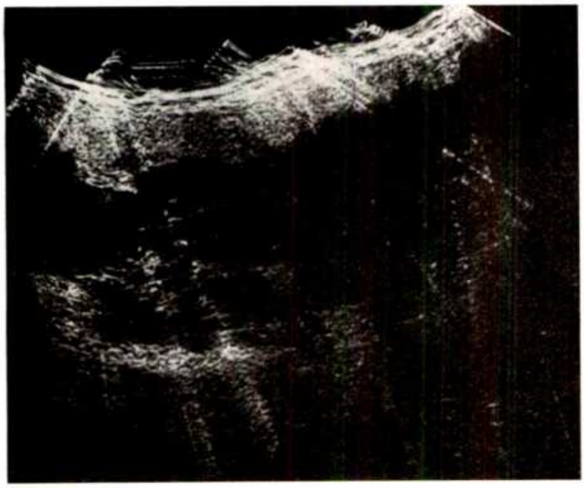


FIG. 7.

Longitudinal scan of kidney in a patient with progressive glomerulonephritis.

be performed and post-mortem was refused. The ultrasonograms (Fig. 7) showed a generalized enlargement of both kidneys and an almost transonic parenchyma. However, the appearance of the collecting system was within normal limits, thus eliminating significant hydronephrosis.

The ultrasonograms taken in the investigations of two patients with polycystic kidney disease showed a generalized enlargement of both kidneys, with an irregular renal outline. Multiple circular transonic areas of variable size throughout the renal substance were visualized (Fig. 8), and no readily identified collecting system pattern of echoes were seen.



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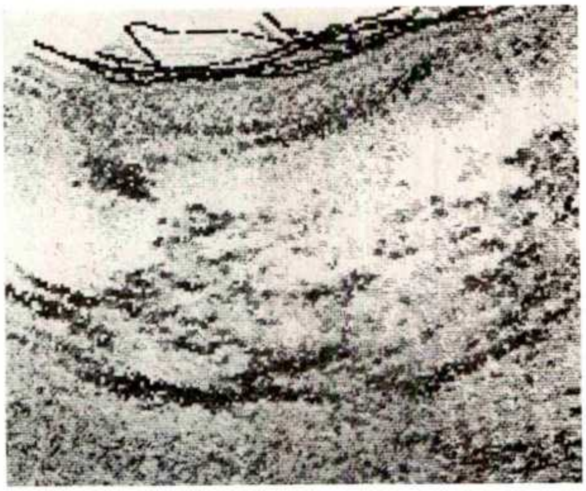

B

FIG. 8.

Longitudinal scan of kidney in a patient with polycystic renal disease. (A) Polaroid. (B) Statos print.

The results of the study investigating the effect of respiration on the quality of the ultrasonic images indicated that the details of renal capsule, ureter and collecting system were sharply defined and easily recognizable during suspended respiration. During shallow breathing, the details became less sharp, and during deep respiration, structural details became very difficult to recognize.

DISCUSSION

Ultrasonic B scanning technology has improved since previous authors have described the "ultrasonic appearance" of the kidney. (Barnett and Morley, 1971; Holm, 1971 and Mountford *et al.*, 1971). These authors had to rely on multiple scans at different gain settings or on examination of the A scan in a particular direction to evaluate the amplitudes of returning echoes. The results that have been demonstrated in this paper show that the new techniques which we are using are capable of displaying anatomical information and echo amplitude information in two-dimensional images.

Using these new "grey-scale" techniques, we have described the ultrasonic appearance of normal and diseased kidneys. Mountford *et al.* (1971) described the parenchyma of the normal kidney as "relatively echo-free". Using "grey-scale" techniques it is possible to record the low amplitude echoes from the renal parenchyma as a light shade of grey in the image. This grey shade due to the echoes from the renal parenchyma has been invaluable in assessing the amplitudes of the echoes depicting other structures in the renal ultrasonograms. Due to variations in transducer output and absorption of ultrasound in differing layers of fat and muscle, it is difficult to make absolute measurements of echo amplitude. Hence the low level parenchymal echoes provide a uniform internal standard for each patient, against which all the other echoes may be assessed. The grey shading has also been useful to define the renal poles in axial scans. The resolution of the "grey-scale" images also allows the imaging of individual calyces and a more satisfactory identification of the renal pelvis.

The scans of the hydronephrotic kidneys were characterized by the appearance of the dilated renal pelvis, which appeared as an area with lower amplitude echoes than the renal parenchyma. These areas correspond to the "ring sign" or "C sign" described by Barnett and Morley (1971). Hence it is now possible to rely on the grey shades in the image rather than the detection of boundaries to obtain diagnostic information. Normally these lower level echoes inside the renal pelvis are shown as transonic areas in our scans. However, it must be realized that fluid filled spaces do return echoes, although they have very low amplitudes (Shimmins *et al.*, in preparation). If these echoes cannot be demonstrated with any particular equipment, this is due to a lack of ultrasonic power or amplifier sensitivity.

The scans of kidneys with neoplastic tumours have usually shown that the tumour tissue returns echoes which have the same or greater amplitude than echoes from the renal parenchyma. There is also usually some bizarre structure of echoes in the tumour space. This allows easy differentiation between tumour and cyst. There is usually no clear boundary between tumour tissue and normal renal parenchyma, although the gradual transition between normal parenchyma and tumour tissue can be clearly identified using this grey scale technique. The difficulty of distinguishing between neoplastic tissue and cyst is illustrated by Mountford *et al.* (1971) who did not use "grey-scale" techniques. They used two observers, one of whom only identified five out of nine cases of cyst and three out of five cases of neoplasm.

The scans of polycystic kidneys were again characterized by apparently transonic areas due to fluid filled spaces, which appeared as echo free areas on our scans as the display is adjusted not to include these very low amplitude echoes. In most cases of polycystic renal disease little normal parenchyma remains and a difficulty sometimes exists in assessing the amplitude of echoes from the cystic spaces. However, in less advanced cases there are areas of normal renal parenchyma. One of the cases imaged in this study was initially diagnosed as normal using a non "grey-scale" scanning system but was subsequently found to be a case of moderate polycystic renal disease by the "grey-scale" technique.

The images obtained from the patient with glomerulonephritis show lower amplitude echoes from the renal parenchyma than we would have expected from a normal kidney. The presumed reason for this is that the parenchyma is now oedematous and therefore returns lower amplitude echoes than normal renal parenchyma.

The longitudinal scans from the patient with a duplex collecting system demonstrated clearly two separate clumps of collecting system echoes. This provides additional evidence that the central clump of echoes seen in the longitudinal scans of normal kidneys is due to the collecting system.

All the "grey-scale" images obtained using the Tektronix 611 display of the Nuclear Enterprises 4102B Diasonograph and the digital analysis and display system were characterized by high resolution and information content. However, the non-integrating nature of the digital system and the digital analysis performed on the images provided more acceptable images. Hence the results described in this paper are largely based on the display from the digital system. Such scans in some respects require more care than is normally taken to maintain good registration. The ultrasonic transducer must be very carefully aligned so that the acoustic and electrical axes are coincident and the patient must suspend respiration during scanning. All of the scans which were made with patients in shallow and deep respiration showed markedly inferior resolution. Accepting these points it was, however, easy to obtain high quality images with the digital "grey-scale" system due to the absence of integration of the display and to the reliability of the digital analysis of the data. It was not necessary to use complicated scanning techniques to avoid integration effects in the image, and relatively untrained personnel were able routinely to produce good images.

These initial studies have demonstrated the potential of improved "grey-scale" renal ultrasonograms. It is now possible to make sharp, grey-shaded images rather than ultrasonograms only showing boundaries. The pulse height information included in such grey-scale images is extremely useful to the diagnostician. However, further investigations are required to demonstrate those areas of investigation in which the new "grey-shade" ultrasonic imaging techniques are clinically most useful.

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Technical note

A simplified method for demonstrating the profunda femoris artery

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(*Received June, 1975*)

Atherosclerosis of the lower limb frequently involves the origin of the profunda femoris artery (Martin *et al.*, 1968). However, radiological demonstration of its involvement is often long and tedious, the method of Beales *et al.* (1971) requiring separate femoral artery punctures. We feel that the technique described below offers significant advantages while at the same time giving diagnostic radiographs.

METHOD

Routine translumbar aortography was first undertaken to demonstrate the lower limb vessels. Then with the patient still prone and the translumbar needle still in position oblique views were obtained on both sides in nine patients and on one side in each of two patients.

Using either a grid positioned at 90 deg. to the longitudinal axis of the table, or a tin filter, a 24 × 30 cm cassette was placed longitudinally under the patient with its mid point at the level of the greater trochanter and with half the cassette remaining clear of the patient laterally. The tube was positioned on the opposite side of the patient and centred on the cassette at an angle of 45 deg. to the vertical. In practice this was achieved by centring on a point mid-way between the natal cleft and the opposite greater trochanter as shown in Fig. 1.

Because of the arrangement of the X-ray machine installed in the room in which the procedure was undertaken it was only found possible to use this machine for one of the oblique views. A portable machine was therefore used for the other oblique and this was found to be quite adequate. Control films were obtained either at the time of the procedure or on the day before.

For each oblique view 15 ml. of Angiografin was injected through the translumbar needle and a single film exposed. Timing of the exposure was judged from the main run.

RESULTS

Of the twenty profunda femoris arteries demonstrated, the origin was found to be narrowed in nine (45 per cent) and in six (30 per cent) of these the prone view failed to demonstrate the narrowing. In two of the limbs examined there was a complete block of the superficial femoral artery immediately distal to the origin of the profunda femoris and the exact site of the obstruction was only demonstrated on the oblique views.

DISCUSSION

Despite earlier reports to the contrary (Margulis *et al.*, 1957; Leeds and Gilfillan, 1961) it is now accepted that the profunda femoris artery provides an important collateral supply to the ischaemic limb and that profundaplasty is often the procedure of choice (Martin *et al.*, 1968; Bernhard *et al.*, 1974; Morris *et al.*, 1974).

Because the profunda femoris artery arises from the postero-lateral aspect of the common femoral artery prone views taken at translumbar aortography usually superimpose the origins of the superficial

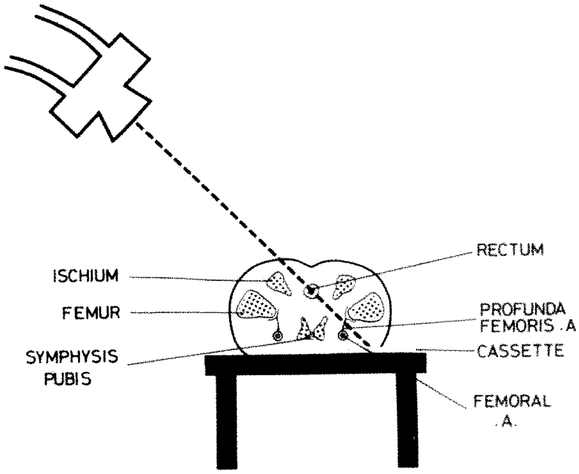

FIG. 1.

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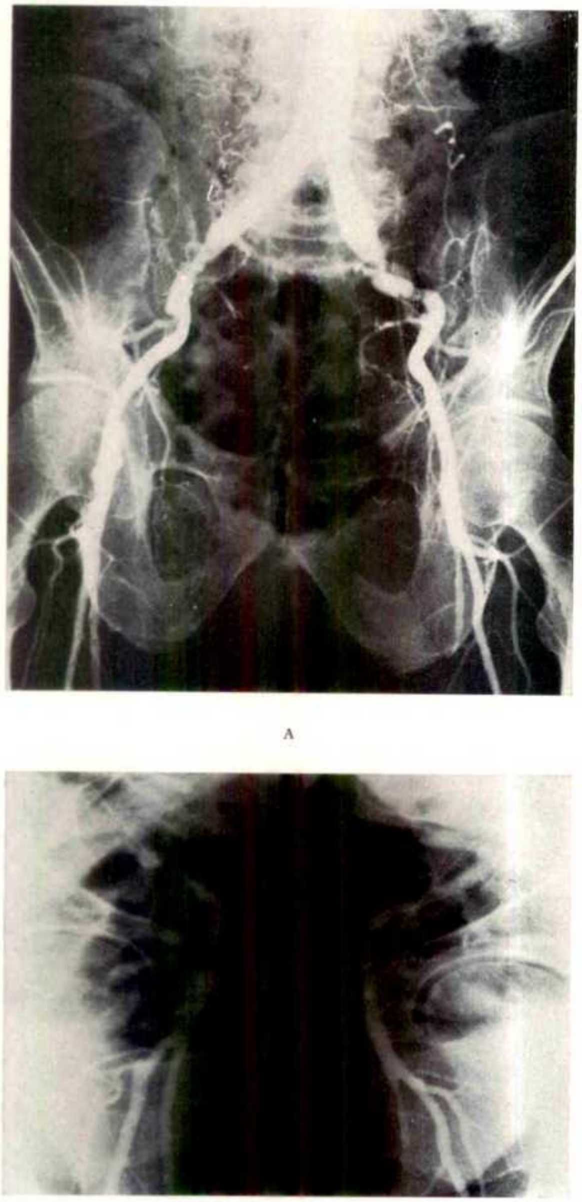
femoral and profunda arteries. Beales *et al.* (1971) showed that by using an oblique view, 39 per cent of profunda origins were narrowed. Our experience confirms this finding.

The technique used by Beales *et al.* required separate femoral artery punctures to be made after the translumbar examination. The addition of this procedure particularly if undertaken bilaterally adds considerbly to the time taken and frequently doubles the total period of anaesthesia. In a busy general department where a number of such investigations need to be carried out at one session this may not be acceptable.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B

FIG. 2.

Prone oblique views eliminate many of these disadvantages while the quality of films, although obviously not as good as those obtained with direct femoral puncture, are quite adequate radiologically (Fig. 2A and B). In practice we have found that the average time taken for a translumbar aortogram and bilateral profunda views has been 30 to 45 minutes.

In all our cases the procedure was carried out under anaesthesia and this enabled a long time exposure to be used (one to two seconds). Because of the frequent difficulty in judging the flow-rate to the upper thigh this long time exposure gave a greater latitude to the procedure and usually enabled us to proceed with the oblique views before the prone view was available, further cutting the overall time of the procedure. The incident skin dose of radiation was found to be between 1 and 3 rad per side.

The total volume of contrast was not significantly increased compared with the method of Beales *et al.*, 15 ml. of Angiografin being quite sufficient to produce diagnostic pictures.

ACKNOWLEDGMENTS

I wish to thank Dr. M. G. Scott and Dr. J. McIvor, of Hillingdon Hospital and Professor R. E. Steiner of the Royal Postgraduate Medical School, London for their encouragement, and Mrs. J. Stillman for the measurements of radiation dose. In addition I would like to thank all the many radiographers who showed enormous patience during the development of this method.

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Case reports

Transcatheter arterial embolization in a patient bleeding from a renal neoplasm

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The ability to selectively catheterize and embolize arteries supplying bleeding points is being used with increasing frequency. The technique has been used successfully to control bleeding following renal biopsy (Bookstein and Goldstein, 1973; Rizk *et al.*, 1973) and in the pre-operative treatment of renal adenocarcinoma (Almgard *et al.*, 1973; Goldstein *et al.*, 1975b). This report describes the selective catheterization of the right renal artery and injection of barium sulphate to stop bleeding from a renal neoplasm.

CASE REPORT

An 82-year-old man presented in 1973 with haematuria, and a hypernephroma was found on excretory urography, confirmed by retrograde pyelography. He had a large liver, ascites, gross chronic bronchitis and emphysema with cor pulmonale. The tumour was not removed because of the patient's general debility.

He was re-admitted in 1975 with gross haematuria and clot retention. An emergency selective right renal arteriogram was performed using a No. 8 French "Cordis" catheter with an end hole only. Thrombus mixed with amino-caproic acid was injected until a total of 4 g amino-caproic acid had been used.

On fluoroscopy, the tumour vessels were still patent, so the guide-wire was manipulated in the renal artery to traumatize the endothelium, and more thrombus mixed with fat obtained from the groin incision was injected. Fluoroscopy showed that tumour vessels were still partially patent, and 4 ml. Micropaque (barium sulphate suspension) mixed with 2 ml. of thrombus was injected slowly under fluoroscopic control. Barium appeared to lodge in the renal tumour vessels, no barium was seen in the renal veins, and there were no ill effects. More Micropaque was injected slowly as the tumour vessels were still partially patent, and when 8 ml. had been injected, the patient complained of breathlessness. Injection was stopped, the patient was sat up, and the catheter was removed. A chest X ray taken immediately showed no change since the film taken on the previous day. The patient continued to be hypotensive and breathless for several hours, but then improved. The haematuria became less the day after the examination and stopped within a week.

The patient died three months later from bronchopneumonia. At autopsy the tumour in the upper pole of the right kidney contained extensive areas of necrosis and haemorrhage. The calyces and the main renal vessels were not invaded.

DISCUSSION

Goldstein and his colleagues (1975a) advocated the use of transcatheter arterial embolization to control blood loss from neoplastic tissue in the gastrointestinal tract and uterus, in patients who were poor surgical risks. Our patient had nearly died following a general anaesthetic because his chronic bronchitis and emphysema were so gross, and this, together with his age, provided contra-indications to surgery.

Thrombus did not stop the bleeding in our patient but has frequently proved successful (Ring *et al.*, 1973; Bookstein *et al.*, 1974; Reuter and Chuang, 1974; Goldstein *et al.*, 1975a). Subcutaneous fat (Rizk *et al.*, 1973; Goldstein *et al.*, 1975a) and amino-caproic acid were also ineffective. No gelfoam (Goldstein *et al.*, 1975b) or suitable leadshot (Rizk *et al.*, 1973) were available, and minced muscle was not used (Almgard *et al.*, 1973). "Micropaque" was

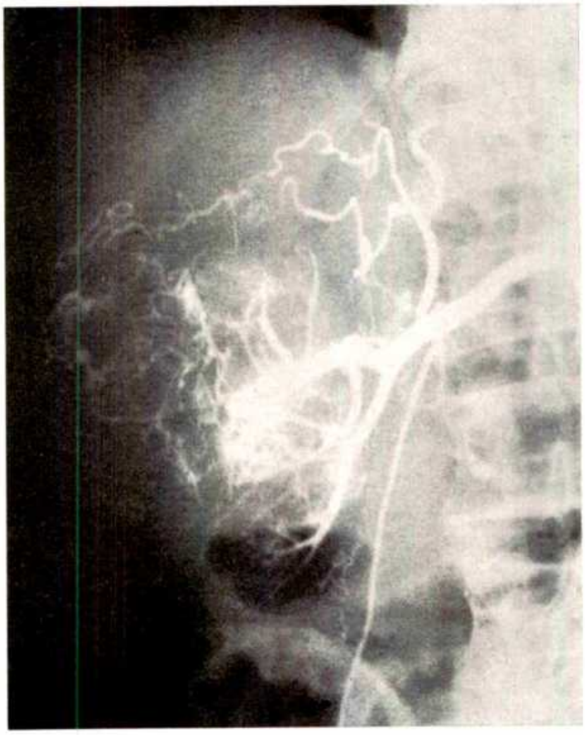

FIG. 1.

Selective injection of barium sulphate into the right renal artery showing the large renal tumour.

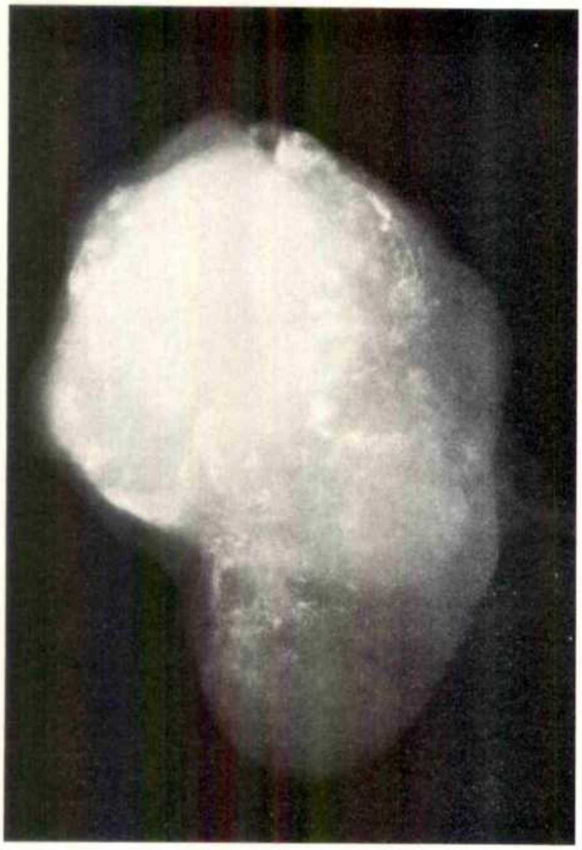

FIG. 2.

X-ray of the post-mortem specimen of the right kidney showing barium still in the renal neoplasm.

used cautiously in a final attempt to stop the bleeding as barium sulphate suspension has been used to infarct the kidney (Goldin *et al.*, 1974). The particle size (0·066 μm to 0·76 μm) (Goddard, 1970) was obviously small enough to allow some of the barium to pass through the tumour vessels to the lungs, producing breathlessness, but no radiologically detectable changes. Much of the barium stayed in the renal tumour (Figs. 1 and 2) helping to prevent bleeding, until the patient died of other causes, although some of the barium had been taken up by the spleen (Fig. 3). Epinephrine was not used, but Rosch and his colleagues (1972) found that infusion of epinephrine before and after the injection of clot prevented fragmentation of the clot.

The large blood flow through the neoplastic kidney made embolization difficult, and although barium proved successful in our patient, it should only be used as a last resort because it may embolize to the lungs. In view of the increasing use of emergency therapeutic arterial embolization, it is worthwhile having such materials as oxycel autogenous clot (Bookstein *et al.*, 1974) readily available.

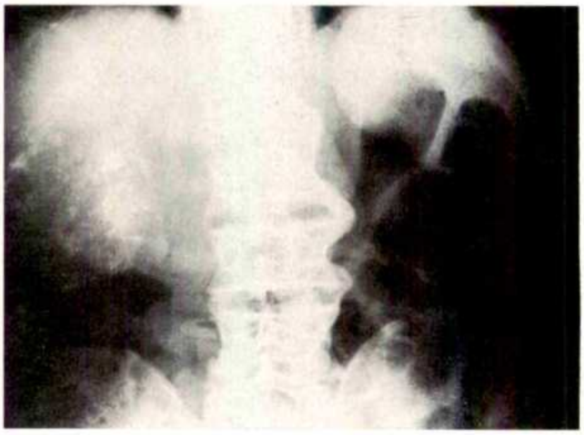

FIG. 3.

Abdominal film taken seven days after the injection of barium sulphate suspension into the right renal artery. There is barium sulphate in both the tumour of the right kidney and the spleen.

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I would like to thank Mr. J. C. Smith, Consultant Surgeon, for his encouragement, the Medical Illustration Department, The Radcliffe Infirmary, for preparing the illustrations, and Dr. M. S. Dunnill for allowing me to X ray the post-mortem specimen.

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Tuberculoma of the pericardium

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(*Received May, 1975*)

Pericardial diseases may mimic specific types of cardiac chamber or great vessel enlargement. This paper presents a very rare entity, tuberculoma of the pericardium, which was mis-diagnosed radiographically as left atrial enlargement.

Case history

A 41-year-old white male complained of "congestion" and heaviness in his upper chest. The patient's medical history included several bouts of childhood pneumonia, and bronchiectasis was diagnosed at the age of 10. The patient's father died of tuberculosis. At 22 years of age the patient developed progressive chest-pain and dyspnoea on exertion, and two years later he underwent pericardiectomy for calcific constrictive pericarditis.

He was well until age 41 when he developed palpitations and left anterior chest pains. There were no other symptoms. On physical examination, his blood pressure was 115/80 with a pulsus paradoxus of 5 mm Hg. The pulse was 80 and irregular. Cardiac examination revealed somewhat distant heart sounds without S_3 or S_4. Electrocardiography revealed atrial fibrillation with a ventricular rate of 90.

Chest radiography revealed cardiomegaly (Fig. 1). The double density behind the right cardiac border on the postero-anterior projection and the rounded bulging of the posterior cardiac contour on lateral projection was interpreted as left atrial enlargement. Left and right ventricular

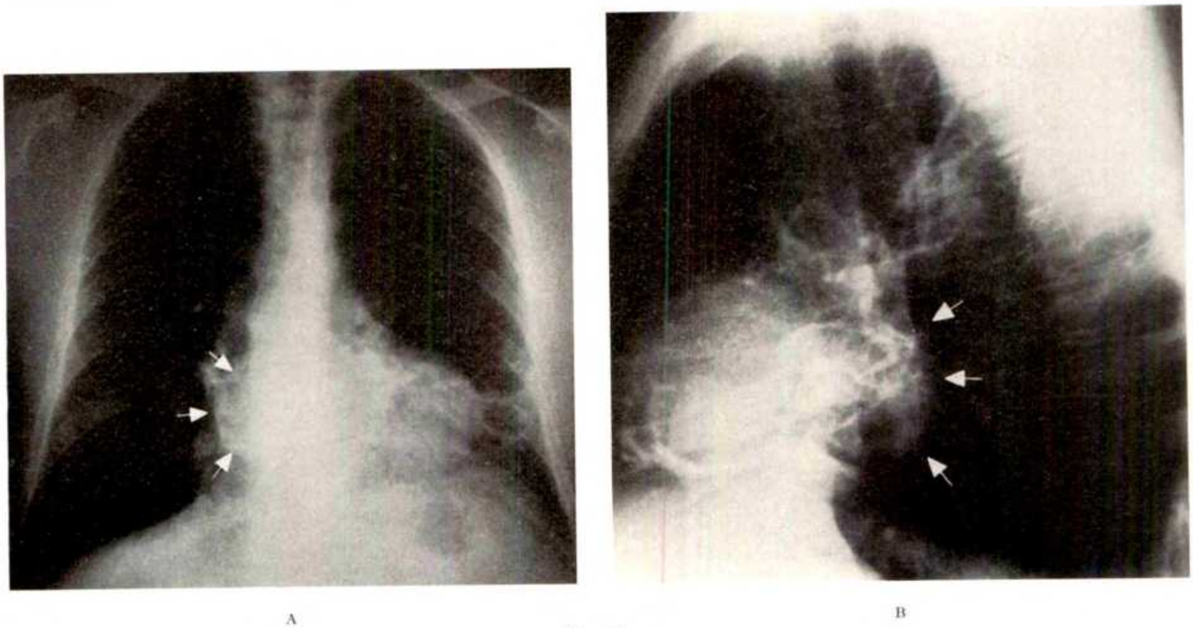
A B

Fig. 1.

Chest radiographs

(A) The postero-anterior view reveals a double density (arrows) behind the right heart border.

(B) On the lateral view, this lesion is visible posteriorly. Note bronchiectasis and calcification of the pericardium.

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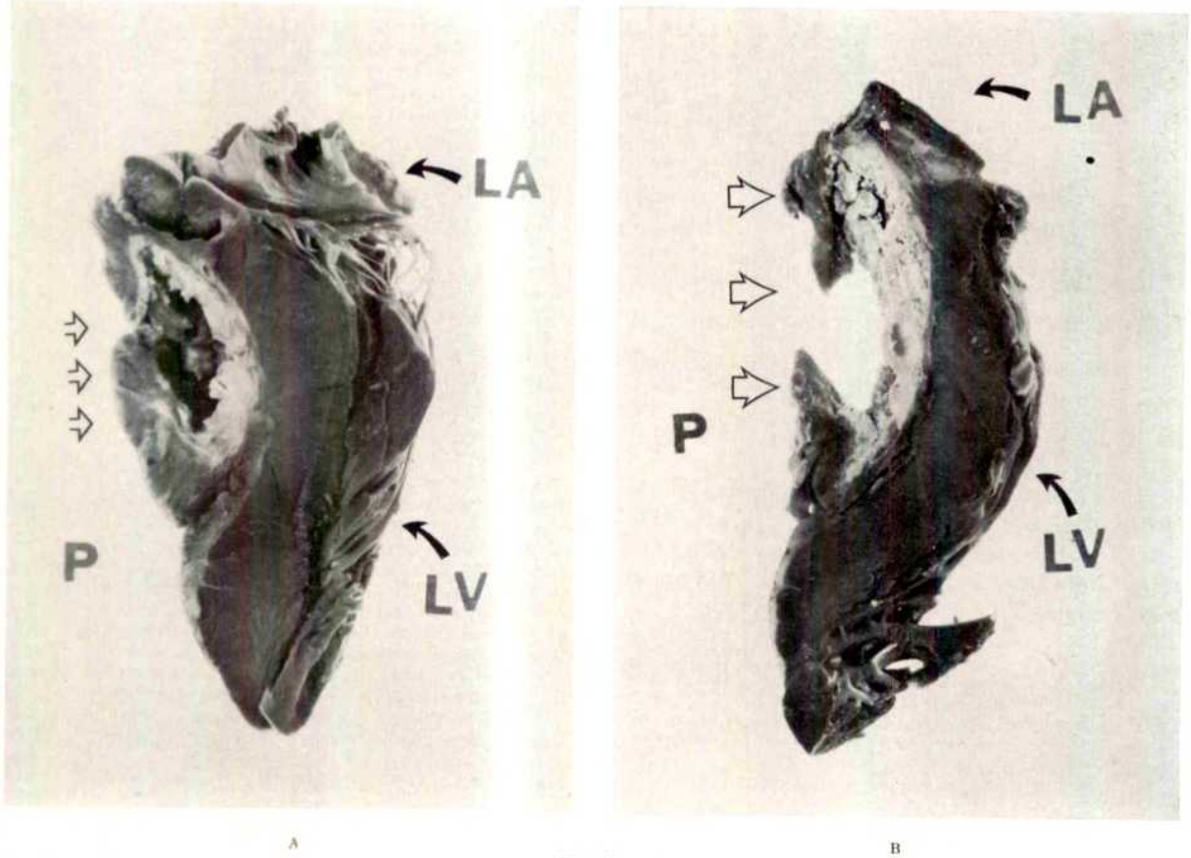

FIG. 2.

(A and B) Pathology specimens of the heart. A 5 cm caseating abscess (open arrows) with central cavitation is located below the atrioventricular groove on the posterior aspect of the heart. LA = left atrium; LV = left ventricle; P = posterior.

enlargement was also suggested. Pericardial calcifications and bronchiectasis were noted. The X-ray impression was that of cardiac chamber enlargement consistent with chronic mitral disease. The patient was treated with digitalis and quinidine for control of his atrial fibrillation and discharged.

The patient returned to the clinic in late 1972 with hepatic adenocarcinoma. After a rapid downhill course, death occurred in February 1973. Autopsy findings included a multicentric hepatoma replacing the left lobe of the liver and widely dispersed throughout the right lobe. This was superimposed on mild inactive cardiac cirrhosis presumably secondary to previous constrictive pericarditis. Saccular bronchiectasis was present in the lingula and a calcified granulomatous focus was found in the left lower lobe.

The heart was slightly enlarged but had a normal configuration. It was firmly fixed to the anterior chest wall and lungs by adhesions. The tricuspid, pulmonary and aortic valves were normal. The tip of the papillary muscle attached to the posterior leaflet of the mitral valve had a focal adhesion. All four cardiac chambers were normal in size and wall thickness. No areas of infarction were present. The coronary arteries showed only minimal atherosclerotic changes. The previous pericardiectomy was evident. A 5 cm calcified abscess was present posteriorly at the reflection of the pericardium on the pulmonary veins (Fig. 2). This was a granulomatous lesion with caseating necrosis. Attempts to culture the acid-fast bacillus were unsuccessful.

DISCUSSION

Tuberculomas involving the heart (Anders, 1902; Pomerance, 1963), and in particular the pericardium (Liverud, 1949; Pipiia and Chikovani, 1970), are exceedingly rare. In a review of the world's literature of the past 50 years, we found only one other well-documented case of pericardial tuberculoma. Pipiia and Chikovani (1970) reported a 29-year-old woman who presented with shortness of breath, palpitations, generalized weakness, and left chest pain. Radiography demonstrated an oval density 6 × 4 cm in diameter adjacent to the base of the heart; the lesion was inseparable from the cardiac silhouette on several projections. At surgery the 8 × 6 cm caseating tuberculoma was found to originate from the parietal pericardium at the root of the aorta.

In our case, surgical removal of the scarred pericardium at the reflection over pulmonary veins had not been attempted at pericardiectomy because of the hazard of haemorrhage (Ellis *et al.*, 1971). It

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was in this region that the patient's tuberculoma developed. Schepers (1962), in a comprehensive treatise on tuberculous pericarditis, asserts that the demonstration of acid-fast bacilli in tissue or culture is not necessary for the diagnosis of tuberculous constrictive pericarditis. In this particular patient the large caseating granuloma makes tuberculosis the most probable aetiology.

Pericardial diseases most commonly lead to generalized cardiac enlargement (Schepers, 1962; Ebert, 1969; Hackel, 1972) but may cause only a localized change in the cardiomediastinal silhouette. The more common lesions which may yield the misleading radiographic signs shown in our patient include congenital pericardial defects (Schepers, 1962; Ebert, 1969; Haider *et al.*, 1973; Haas, 1939), benign neoplasms, and non-infectious inflammatory lesions (Bozer and Saylam, 1973). These pericardial lesions often cannot be separated with routine radiographic techniques, but they should be emphasized in the differential diagnosis whenever the clinical findings do not correlate with the radiographic findings.

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Intrathoracic Hodgkin's disease presenting as hypertrophic osteoarthropathy

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The association of hypertrophic osteoarthropathy with Hodgkin's disease is rare. We report a patient who is unique in that she presented with the clinical features of hypertrophic osteoarthropathy, the Hodgkin's disease being discovered only after investigation. Objective clinical and radiographic improvement of hypertrophic osteoarthropathy was observed after chemotherapy of the lymphoma.

CASE REPORT

A 16-year-old girl presented with a two-month history of clubbing of the fingers and swelling of the ankles. On examination she was anaemic and pyrexial. She had obvious clubbing of fingers and toes, and tender swelling of ankles and wrists. The skin was ichthyotic and no lymph-nodes were palpable. Peripheral blood examination showed anaemia (7·9 g/100 ml. microcytic normochromic) neutrophil leucocytosis (11,500/mm^3) lymphopenia (1,000/mm^3) and an elevated ESR (120 mm/hour).

The chest X ray showed lobulated masses lying in the right hilum and in the superior mediastinum, characteristic of lymph-node enlargement (Fig. 1A). There was no evidence of any lesion in either lung. The findings were thought most likely to indicate the presence of a lymphoma. Many of the long bones showed periosteal new bone formation, this being most evident in the wrists and ankles, but also affecting many of the phalanges (Fig. 2A) and the femora. In the clinical context this appeared to be due to hypertrophic pulmonary osteoarthropathy. Lymphography was carried out demonstrating enlargement of the upper para-aortic lymph-node chains with the presence of multiple small filling defects within the enlarged lymph-nodes. These findings were thought to be compatible with the

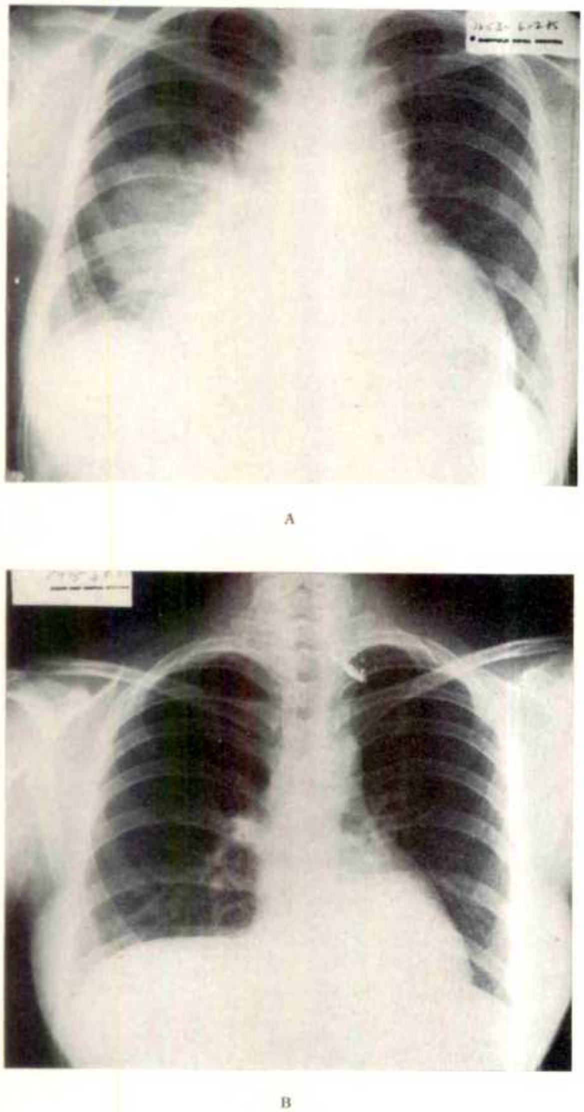

FIG. 1.

Chest radiographs.

(A) Mediastinal and hilar lymph-node enlargement.

(B) Resolution after treatment.

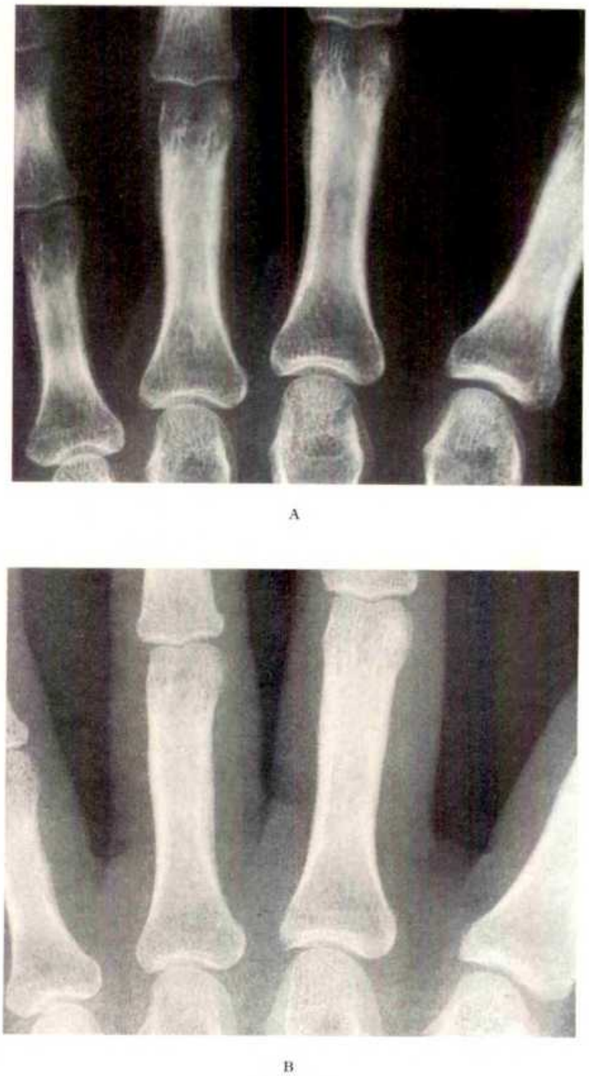

FIG. 2.

Hand radiographs.

(A) Changes of hypertrophic osteoarthropathy in phalanges.

(B) Improvement after treatment.

presence of lymphomatous infiltration. Scintiscans of the liver and spleen with Tc–S colloid showed no abnormality.

The patient subsequently underwent diagnostic laparotomy with splenectomy, and a diagnosis of Hodgkin's disease (nodular sclerosing type) was confirmed from the para-aortic lymph-node biopsy. The liver and spleen were not involved. She was staged 3B (Ann Arbor classification) and was started on cyclical quadruple cytotoxic chemotherapy (nitrogen mustard, vincristine, procarbazine, and prednisolone). She responded well and within three months digital clubbing had regressed to normal.

Radiographs obtained at this stage showed marked regression of the hilar and mediastinal lymphadenopathy (Fig. 1B). The periosteal new bone formation also showed considerable regression but remained visible in the wrists and to a lesser extent in the phalanges (Fig. 2B). The abdominal lymph-nodes also showed response to chemotherapy.

DISCUSSION

Mediastinal involvement with lymphoreticular malignancy is common but a search of the literature has revealed only nine well-documented cases of hypertrophic osteoarthropathy in association with intrathoracic lymphoma (Weber and Ledingham, 1909; Lewis, 1955; Hammersten and O'Leary, 1957;

Adler and Sharman, 1970; Molyneaux, 1973; Shapiro and Zvaifler, 1973, Kay *et al.*, 1974).

In only one of these cases (Lewis, 1955) was hypertrophic osteoarthropathy a presenting finding and this patient had obvious generalized lymphadenopathy. In one other case (Molyneux, 1973) there was objective improvement in hypertrophic osteoarthropathy after therapy of the lymphoma. Our patient is characteristic of the majority of other cases reported in that she is young and shows the typical clinical and radiographic changes of hypertrophic osteoarthropathy. She is unique in that she presented without overt evidence of Hodgkin's disease which was confirmed only after diagnostic laparotomy. Clinical and radiographic improvement in hypertrophic osteoarthropathy has been observed after cytotoxic chemotherapy of her lymphoma.

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Book review

Year Book of Diagnostic Radiology. Edited by Walter M. Whitehouse, pp. 479, illus., 1975 (Chicago, Year Book Medical Publishers, Inc.), £11·85.

As its new title suggests, the current issue of the *Year Book* is devoted entirely to diagnostic radiology, the therapy section having moved to a new home in the *Year Book of Cancer.* This change is entirely appropriate, reflecting the increasing association of therapeutic radiology with oncology, and the separation of the somewhat artificial links that have existed between the two major branches of radiological medicine.

Old friends of the *Year Book* will be relieved to learn that the change in its composition has not affected its flavour. Under the continued editorship of Dr. Whitehouse the book provides detailed abstracts of recent key references in each of the main disciplines of diagnostic radiology. The selection of the papers abstracted is necessarily somewhat arbitrary, but nevertheless continues to be remarkably comprehensive, and the pithy editorial annotations to some of the abstracts from the more enthusiastic papers serve to keep the reader's feet on the ground.

As usual many of the sources of the abstracts are non-radiological which is of particular help to those who find it difficult enough to keep abreast of the current literature in radiology, never mind the rest. The composition of the present issue reflects the current trends in radiology: the expanded section on technical developments includes abstracts of some fundamental papers on computerized axial tomography, and clinical aspects of the same technique are further developed in the section on neuroradiology. The very rapid expansion in this field of diagnostic radiology means that the descriptions contained in the current issue of the *Year Book* have to some extent been already outdated by more recent technical developments. This is inevitable in any subject undergoing such rapid changes and is a drawback well recognized by the editors themselves. A further example of the growth of relatively new sub-specialties is given by the fact that ultrasound is now accorded a chapter of its own, and this is well worth perusing by anyone working in this field. The angiography section, edited by Dr. Joseph Bookstein, includes articles on the localization of bleeding and the therapeutic use of the catheter for embolization, and exemplifies the attention given in all sections of the book to items that are of topical interest.

The book remains essential reading for those seeking rapid and pertinent coverage of current radiological trends, and is a valuable source of references for the new reader seeking an introduction to the literature pertaining to a particular field of diagnostic radiology.

D. ALLISON.

1976, *British Journal of Radiology*, 49, 650

Proceedings of The British Institute of Radiology

High-energy apparatus for radiotherapy

Abstracts of papers read at a meeting held at Institute House, 32 Welbeck Street, London W1M 7PG on Thursday, November 20, 1975

Apparatus, present and future, by F. T. Farmer
A clinical view, by K. E. Halnan

APPARATUS, PRESENT AND FUTURE

By F. T. Farmer
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The main advantages of megavoltage therapy, namely high-penetration, surface build-up and diminished scatter are achieved at the 4 to 6 MV level, and to a comparable degree using Cobalt 60. Such radiation may now be regarded as a minimum requirement for a modern radiotherapy department. Higher voltages have found a place, either as X-ray or electron sources, and linear accelerators working in the 8–12 MeV range and betatrons in the 18–45 MeV range are now well known. The latter have particular value for electron therapy; photon dose-rates tend to be low compared with those from linear accelerators. The merits of such high energies have to be weighed against cost. Evidence from Toronto and Houston has shown that 22 MV X rays have a significant advantage over Cobalt 60 for treatment of carcinoma of the cervix; ten-year survival rates are quoted as 38 per cent and 18 per cent respectively. Cobalt 60 is regarded as unacceptable by these workers.

Neutron generators of the D–T type are now coming into operation at Manchester and Glasgow, following experience gained with the 7 MeV cyclotron neutrons at Hammersmith. Encouraging results from the latter are presented by Dr. Mary Catterall.

The Microtron operating at 20 MeV is an interesting addition to the range of high-energy equipment.

Looking ahead, higher-energy beams of π-mesons hold fascinating possibilities. Despite the cost, plans are already advanced for setting up a clinical trial with these beams at Stanford, California.

A CLINICAL VIEW

By K. E. Halnan
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Modern 'adjuvant' chemotherapy is effective against microscopic metastases but not against large primary tumours; its success will make good radiotherapy of the main tumour mass more rather than less important. The main factors needed for a routine service unit are *reliability* (the most important), good output and quality, adequate depth dose and beam sharpness. Reliable units now available include cobalt units, linear accelerators, betatrons and cyclotrons. Future units may have better dose distributions or better biological effects or even both; it is suggested that the latter is the more important and that high-energy neutrons from a D–T generator promise more benefit than do π-mesons. Experience of unreliable units makes it undesirable for untried or prototype machines to be installed too soon in hospitals.

The best selection for today is an identical pair of 5–10 MeV linear accelerators, or cobalt units as a close second choice; with a high-energy electron unit, probably a betatron, as a useful ancillary. In the immediate future, the microtron might replace all these but fast neutrons could have more biological advantages.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents.)

THE EDITOR—SIR,

RELATIONSHIP BETWEEN LOG DOSE AND LOG TIME IN RADIOTHERAPY—THE STRANDQVIST LINES

Strandqvist (1944) plotted log dose against log time to obtain a slope representing this relationship for reactions in skin and for control of epidermoid carcinoma of the skin of the face. The impression exists among most radiotherapists that the slope must always be the same. The following discussion, however, indicates that this is not always so.

Suppose that in a certain time T_1 various fraction doses of radiation are given with appropriate numbers of fractions to produce the same biological effect. The isoeffect line might then be represented by AB. Using another time T_2 other fraction doses and numbers of fractions might be used to produce the same biological effect represented by an isoeffect line CD.

Moreover AB and CD could both represent the same effect. If this is so, then a line joining any point P on AB to any point Q on CD will be joining two points of equal effect and thus will be almost certainly an isoeffect line. Such isoeffect lines can have any slope from minus to plus infinity.

Suppose $D = C.\,N^x.\,T^y$ where D is the dose necessary to produce a given biological effect delivered in N fractions in T days and C is a constant representing the biological effect. In this analysis T is defined as the elapsed days plus the average interval between fractions (Orton and Ellis, 1974).

Then if $N = k\,T$

$$D = C.\,(kT)^x.\,T^y$$

$$\therefore\ \text{Log } D = \text{Log } C + x \text{ Log } k + (x+y) \text{ Log } T$$

(*Note:* for treatment five times weekly $5 = k.\,7$, *i.e.* $k = 5/7$

for treatment once weekly $1 = k.\,7$, *i.e.* $k = 1/7$

It is clear that if C and k are constant $(x+y)$ represents the slope of Log D against Log T.

If k is not constant (*i.e.* if the frequencies vary) then even if C is constant (*i.e.* an isoeffect figure) the relationship of Log D and Log T (*i.e.* the slope) is not represented by $(x+y)$

Instead $\text{Log}\dfrac{D_1}{D_2}\Big/\text{Log}\ \dfrac{T_1}{T_2}$ = the slope of the isoeffect line

$$= X\left(\text{Log}\frac{k_1}{k_2}\Big/\text{Log}\frac{T_1}{T_2}\right) + x + y$$

where the subscripts refer to two different schedules. If $k_1 = k_2$. *i.e.* if the frequency of the schedules is the same then the slope is $x+y$. Similarly, it can be shown that the slope of Log D relative to Log N is constant if the frequencies are the same.

Yours, etc.,
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Explanation 1

The reason for using $T^{0\cdot11}$ and $N^{0\cdot24}$ in the NSD equation is explained below, but not in one sentence. It has been explained in papers on the NSD and depends on graphs by Cohen embodying work by various authors.

In the NSD equation the separation of the time from the fractionation effect was effected by considering:

(1) that squamous carcinoma survival represented a tolerance level for the squamous carcinoma cell;
(2) that the squamous carcinoma cell was a model for a normal cell without homeostatic control;
(3) that the difference between the isoeffect slopes for normal skin and for squamous carcinoma represented the effect of external homeostatic control;
(4) that homeostatic control depending on "feedback" depends on time;
(5) that the internal recovery of cells depends on the number and size of fractions;
(6) that in the data of the graphs (i) recovery from sublethal damage is complete between fractions, (ii) the treatment was given five times weekly so that the relation between fraction number is such that the coefficient for the number of fractions is 0·24 instead of 0·22.

Thus $x = 0{\cdot}11$ and $y = 0{\cdot}24$ so that $x + Y = 0{\cdot}35$.

I think by leaving out quantities no such explanations are needed.

Explanation 2

T is best used, as indicated in the letter by Orton and Ellis (1974) as elapsed days + interval between fractions. The reason is the implied assumption of recovery between fractions. If a certain time is allowed for recovery between fractions, then the same time should be allowed for the last fraction. This can result in a difference for the same NSD of the order of 5 per cent in dose when three treatments are given at weekly intervals according to whether the elapsed time of 14 days between treatments is used (3 × 1,090 rad) or the elapsed time and one week is used (3 × 1,040 rad).

When seven treatments are used the difference is between 42 and 49 days and the difference in dose per fraction between 620 and 630, *i.e.* about 2 per cent.

THE EDITOR—SIR,

RECOGNITION OF RADICULOMEDULLARY ARTERIES

Some statements in the figure-captions of the paper "Segmental intervertebral anastomosis in subclavian steal" (*British Journal of Radiology*, R. A. Baker, A. E. Rosenbaum and G. H. Robertson, February 1975) are open to question. Specifically, the vessels indicated as "radiculomedullary branches" in Fig. 2 cannot be such arteries as they course directly downward without a proximal "hairpin" arrangement. A similar question arises regarding the multimetameric vascular structures indicated with arrows and labelled in the legend of Fig. 5A as "bilateral segmental radiculomedullary branches". Arteries which penetrate the intervertebral foramina and are located behind the vertebral bodies are not necessarily radiculomedullary branches. In Bassett's *Stereoscopic Atlas* (Bassett, 1962) from which Fig. 5 is derived, the same vessels are correctly labelled as suppliers of the vertebral bodies. Whether radiculomedullary channels are indeed visualized in Fig. 7 (I would concur here with the authors' qualification of "diminutive") remains, on the face of the evidence offered, *sub judice*.

1976, *British Journal of Radiology*, *49*, 652–653

Correspondence

There is an extensive body of literature on the origin, course and distribution pattern of the radiculomedullary vessels and their distinction from arteries supplying bone, muscle and meninges, as well as from veins. A comprehensive listing of the appropriate references is to be found in a recent review (Di Chiro and Wener, 1973).*

The purpose of the present letter is not to make a fine academic point or to be hypercritical of an article which, in other respects, represents an important contribution by pointing out the importance of horizontal intervertebral anastomoses. These anastomoses do indeed take place both via radiculomedullary branches and, as clearly confirmed and documented in this paper, through non-cord-directed vessels. Rather, this letter continues what I consider by this time a sort of crusade, *i.e.*, insisting that angiographers acquire confidence in the recognition of the radiculomedullary branches, a sometimes tricky affair based on subtle anatomo-radiographic nuances. It is in part, because of lack of familiarity with the appearance of these vessels that a frighteningly large number of postangiographic cord complications occur (Di Chiro, 1974). The majority of serious and permanent complications take place at the time of repeat injection of the angiographic contrast medium. It is obvious, therefore, that the detection of *bona fide* radiculomedullary branches at the first injection may be critical.

Yours, etc.,
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THE EDITOR—SIR,

THE PITUITARY FOSSA—NORMAL OR ABNORMAL?

My attention has been drawn to the recent paper by Drs. H. A. Swanson and G. du Boulay in which they dispute the value of minor variations in the pituitary fossa such as reduplication of the floor or thinning or erosion of the lamina dura, as evidence in favour of the diagnosis of a pituitary tumour. They suggest that by using these criteria as proposed by McLachlan *et al.* (1970) endocrinologists overdiagnose the occurrence of pituitary tumours. My assessment of the data presented by Drs. Swanson and du Boulay leads me to suggest that their conclusions are invalid, and that these radiological signs may indeed be valuable in the appropriate clinical context.

Drs. Swanson and du Boulay report radiological pituitary fossa abnormalities on both plain and tomographical examination in 32 per cent of 85 patients having neurological investigations for non-endocrine indications. As the "final diagnoses" in the patients obtained from perusal of the case notes did not suggest any endocrine abnormalities the patients were deemed to be endocrinologically normal. No endocrine investigations were done, apparently, to confirm this assumption and one might perhaps be allowed to wonder how frequently evidence for minor aberrations of sex function, thyroid status, hair distribution, fertility, menstruation, lactation, etc. were carefully sought, noted and included in the "final diagnoses" in patients with neurological diseases seen at a specialist neurological hospital. Only with the recent advent of sensitive hormone assays have we learnt how frequently important endocrine diseases, especially those involving the pituitary gland may be impossible to diagnose on clinical grounds alone. I am therefore led to the conclusion that the patients studied by Drs. Swanson and du Boulay were not necessarily endocrinologically normal merely because their case notes failed to include an endocrine disease in the "final diagnosis".

One has to consider whether it is feasible that 32 per cent of unselected cases could possibly have abnormalities of the pituitary gland. What is the incidence of unsuspected pituitary tumours found at routine autopsies? While many authors have suggested that the incidence is high, perhaps the most detailed report is that of Costello (1936). He reported an overall incidence of 22·5 per cent in 1,000 cases ranging in age from still-born infants to 99 years. The incidence increased with age to reach a peak in the fifth decade. If we are to compare this series with that of Drs. Swanson and du Boulay we must allow for the relative paucity of patients below the age of 20 and above 70 years in the latter series, and consider only those between 20 and 70 years in that of Costello. The incidence of autopsy-proven pituitary adenomas in this group varied with age between 16 per cent and 37 per cent with an average of 31 per cent, not too different from the 32 per cent found by Drs. Swanson and du Boulay. The latter authors conclude that if the radiological signs are considered individually an incidence of 14 per cent of reduplication of the sellar floor or 16·5 per cent of thinning of the lamina dura on tomography are "surely too high a percentage to be due to unrecognized pituitary tumours". Costello's data suggests that this opinion is not consistent with the experimental evidence.

This problem must surely be put in context. Most endocrinologists would say that in an appropriate clinical framework and when the investigations suggest excessive secretion of a pituitary hormone, then the radiological signs of McLachlan *et al.* (1970) must be taken to indicate the possible presence of a pituitary tumour, and the clinical management organized accordingly. Routine surgical exploration of the fossa using these criteria has confirmed the value of the radiological signs discounted by Swanson and du Boulay (Hardy, 1973). If the signs are ignored the patient may suffer. Thus total adrenalectomy for Cushing's disease without concomitant pituitary irradiation in patients with the radiological signs of microadenomas often results in rapid enlargement of the tumour and hyperpigmentation; pregnancy in patients treated for infertility and hyperprolactinaemia may result in blindness due to chiasmal compression from rapid enlarging of the tumour unless the microadenomas common in this condition are recognized and treated first. Unfortunately too often the signs are ignored and the radiologist reports the fossa to be normal and this is accepted by the clinician.

Certainly such minor changes in the fossa will not be significant in some patients but luckily endocrinology has passed on from being a discipline based merely on clinical evaluation and a look at the X rays. It is highly technologically based science in which accurate diagnoses may be achieved by considering all the evidence—clinical, radiological and biochemical. I hope that not too many radiologists will totally ignore the valuable diagnostic features decribed by McLachlan *et al.* (1970).

Yours, etc.,
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*A chart of the "Arteries of Spinal Cord" is available on request from the Eastman Kodak Company.

1976, *British Journal of Radiology*, *49*, 653

JULY 1976

Correspondence

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THE EDITOR—SIR,

THE PITUITARY FOSSA—NORMAL OR ABNORMAL

Professor Besser's knowledge and experience are to be greatly respected. For all that I reserve my scepticism about the relevance of the X-ray signs which we talk about in our paper. Though I do not doubt that microadenomas are very often associated with visible sellar changes, these changes are so similar to normal asymmetries as often to be indistinguishable.

One can put the point in a slightly facetious way by saying "If a third of a sample of the adult population is suffering from pituitary adenomata is this not the beginning of the end of the human race?" In any case, if radiologists cry "Wolf" at every double sellar floor it will not be long before their reports are ignored.

Yours, etc.,
G. DU BOULAY.

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THE EDITOR—SIR,

NEW TERMINOLOGY NEEDED

There appears to be a lack of suitable names for several recently developed techniques in radiology and nuclear medicine.

An example which comes to mind is the use of the EMI-Scanner. To use the word "emiscan" as a noun is displeasing; as a verb it is even less acceptable—"I emiscan, you emiscan, he, she or it emiscans". Other terms such as section scanner or computer scanner are in common use. Besides being cumbersome there is also a conflict with the tomographic type of isotope scan used, for instance, by Mallard in Aberdeen.

Professor Farmer has pointed out these semantic difficulties to the Nuclear Medicine Committee of the Institute which has decided to ask readers of the Journal for any suggestions about terminology.

Greek and Latin are supposed to confer a degree of respectability and classical scholars of "O" level standard and above are particularly asked to give this problem some thought. Any suggestions should be forwarded to the undersigned.

Positively no prizes are being offered but the winner may have the satisfaction of seeing a word he or she has invented pass into the literature.

Yours, etc.,
J. P. NICHOLSON.

Honorary Secretary,
Nuclear Medicine Committee,
British Institute of Radiology,
32 Welbeck Street, London W1M 7PG.

THE EDITOR—SIR,

ACADEMIC RADIOLOGY

Professor McLachlan has posed some timely questions concerning university departments of radiology (*B.J.R.*, February, 1976). I agree that there should be departments of radiology in the medical schools, and that these are best led and represented by professors of radiology. Centres with university-paid staff seem able to devote much more effort to organized teaching than those without (Baddeley and Middlemiss, 1973).

British universities are notoriously slow in recognizing academic disciplines and there have been too few chairs in radiology. This situation is changing and it is to be hoped that there will soon be at least one professor of radiology in each medical school in the United Kingdom.

Professor McLachlan is concerned with the relationship between the new professors and their Health Service colleagues, who are also "chosen after much thorough inquiry" and "many of whom have outstanding academic records". He holds up the experience of university hospitals in North America and Scandinavia as an example to be followed and claims that "unless we are prepared to appoint professors as heads of departments in teaching hospitals we cannot anticipate the kind of advances in academic radiology we claim we want". He seems to suggest that the National Health Service should abandon the principle that no one should be in authority over Health Service consultants.

Our present professors in radiology are eminent men who in many cases were already successful directors of teaching hospital departments before appointment to their chairs. It is excessive to expect new professors to be pre-eminent in the fields of service commitment, hospital administration, organization of all teaching, all research and university administration. To give even the most capable individual too many powers and responsibilities at once is to threaten his competence (Peter, 1972). Professors of surgery are not responsible for all surgical activities of a district teaching hospital, nor should we make professors of radiology responsible for all the radiological activities.

Surely the basis for a harmonious relationship is that the professor should head his university department and engage himself in the hospital department in his own sphere of expertise alongside his Health Service colleagues. Differing circumstances will dictate whether or not the professor might assume chairmanship of the teaching hospital departments. He should be *primus inter pares* with regard to his own speciality, methods of teaching and the promotion of research. Certainly academic departments and their members must not be sequestrated.

If the professor is unable to engineer desirable changes as a co-equal in the hospital department, it is unlikely in this country, that he would be able to do so as a *Röntgen Meister* of the sort that Professor McLachlan seems to recommend.

Yours, etc.,
H. BADDELEY.

Department of Radiodiagnosis,
Bristol Royal Infirmary,
Bristol BS2 8HW.

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McLACHLAN, M. S. F., 1976. Radiology now. Academic radiology. *British Journal of Radiology*, *49*, 103–104.

1976, *British Journal of Radiology*, 49, 654

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

First Meeting of the World Federation of Ultrasound in Medicine and Biology

This meeting, to be held August 3–7, 1976 in San Francisco is the third world congress on ultrasonics in medicine.

Reduced registration fees are payable by members of the international sub-group of the British Medical Ultrasonics Group.

Further information from: 1st W.F.U.M.B., PO Box 25606, Oklahoma City, Oklahoma 73125, U.S.A.

For information about B.M.U.G. contact the General Secretary, B.I.R., 32 Welbeck Street, London W1M 7PG.

A Symposium on Radioisotopes in Cardiology

Jointly organized by The British Institute of Radiology and the British Cardiac Society will be held on Wednesday, September 29, 1976, at the Greenwood Conference Centre, Guy's Hospital.

Registration fee: £9·50 including lunch, morning coffee and afternoon tea.

Further details and registration forms will be available from The Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Attendance may be limited and registrations will be accepted in the order they are received.

European Symposium on Gynaecological Cancer

This meeting to be held at the Hilton Hotel, Athens, on October 7–8, 1976, under the auspices of the European Association of Radiology.

Further information from: EAR Symposium on Gynaecological Cancer, Areteion Hospital, 76V as. Sophias Avenue, Athens 611, Greece.

8th Congress of the Society of Hungarian Radiologists and 12th Annual Meeting of the European Society for Radiation Biology

To be held in Budapest, Hungary, October 19–22, 1976.

For further information please contact the Congress Office (H-1361 Budapest, PO Box 32, Hungary).

Autumn Meeting North of England Branch of B.I.R.

The autumn meeting of the North of England Branch of the British Institute of Radiology will be held at the Children's Hospital, Sheffield, on Saturday, October 30.

This is the Centenary year of the Children's Hospital and the staff will be presenting short papers. If anyone fails to receive a notice of this meeting by post would they please inform the General Secretary of the B.I.R.

British Medical Ultrasonics Group

The Annual Meeting of the British Medical Ultrasonics Group will be held in Dundee on December 20–21, 1976.

Papers will be presented on all aspects of diagnostic ultrasound and there will be an associated commercial exhibition.

Further details from: The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiation Protection: An Example of Action Against Modern Hazards

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colegio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Obituaries

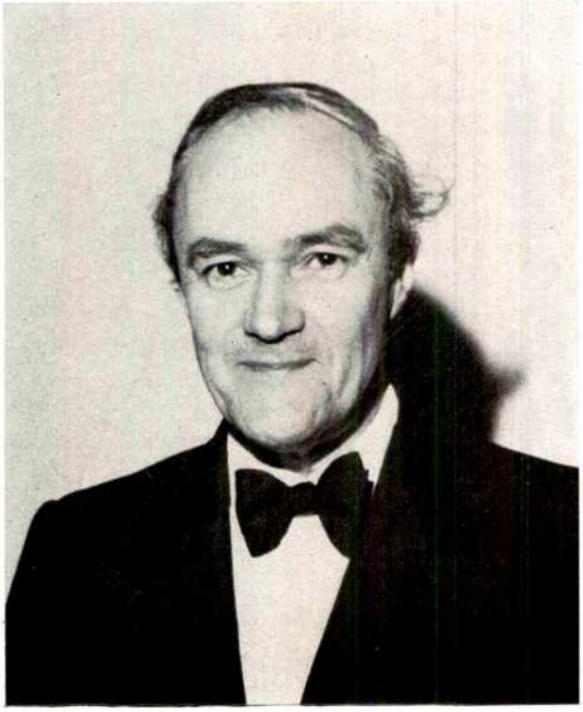
Raymond Oliver, M.A.(Oxon.), B.Sc., D.Sc., F.Inst.P., F.Inst.Biol., F.I.E.E.

Professor of Medical Physics at the Royal Postgraduate Medical School, died on Friday, March 5 1976, in his 55th year.

He started his scientific career at the National Physical Laboratory, but already, in 1945, decided to turn towards medical physics and joined the Department of Radiotherapy at the London Hospital. In 1950, he came to Oxford with Dr. Frank Ellis, to the new Radiotherapy Department then set up there, as Principal Physicist and later as Radiation Protection Officer and Lecturer in Medical Physics of the University of Oxford. In 1971, he was offered the Chair of Medical Physics at the Postgraduate Medical School, which he occupied until his untimely death.

Ray Oliver was an exceptional person in many respects. His scientific curiosity was inexhaustible. Apart fron his books on *Basic Physics in Radiology* (with L. A. W. Kemp) and on *Radiation Physics in Radiology*, his output of over 150 scientific papers covered a very wide field of specialities; from radiation physics and dosimetry to isotope methodologies, problems of diagnostic radiology, all aspects of radiotherapy, cell population kinetics, autoradiographic analysis of cellular physiology, haemopoiesis, basic radiobiological mechanisms (from plant tissue to mammalian cells and cell populations), to thermography and the biological effects of ultrasound. Many of his models are classical stepping stones of science, and it may be invidious to name a field to which he contributed most; my bias certainly would pick on fundamental radiobiology and on cell population kinetics, to which he made long lasting significant contributions.

His scientific reputation took him to committees and councils of several learned societies: to the Presidency of the Hospital Physicists' Association, Chairmanship of the British Radiological Protection Association, Honorary membership of the Royal College of Radiologists, Council member of the British Institute of Radiology, member of the Scientific Committee of the Cancer Research Campaign, Council member of the Society for Radiological Protection, Committee member of the I.C.R.P., and many others. He was a well-known and respected figure at international conferences—his students came from close and afar. He had an easy way of getting on with people, and has built up a happy laboratory at Oxford and a happy department at Hammersmith.



I had the good fortune of collaborating with him for over a decade—a very happy, very satisfying and exciting decade. His grasp of a scientific problem—irrespective of the speciality—was almost uncanny, especially as he did it, like everything else, with such utter unfussiness. He would listen, ask a few, very basic, questions—then out would come the old tubular slide-rule, a sheet of paper, and an elegant solution or highly constructive suggestions! But he was not only a first-class theoretician, but a superb physical experimentalist—designing, constructing and using complex electronic apparatus was child's play for him. His laboratory and office was almost a place of pilgrimage for all of us; radiotherapists, radiologists, radiobiologists, cell biologists, physicians, biochemists, physicists alike. Ever ready to listen and help—how has he found the time for all . . . ? What a pleasure it was to work with him.

He was a real teacher. His lectures to students or to specialists, his explanations to collaborators, were characterized by their lucidity. He had the gift of making complicated problems and subjects sound simple—the simplicity of the explanation frequently hid the scholarship behind it all. The same character shone through his committee work—quiet, very effective. And he was a friend, a rare, warm human being, ready to help with word or action—an utterly dependable friend. If I could criticize him, it would be for his almost self-effacing modesty—but in a sense, this itself was a sign of the quiet strength of his character: he did not need to assert himself.

The way he carried the burden of his disease—the outcome of which was very familiar to him—was an incredible testimony of the strength of his personality, a strength to which his very happy family life greatly contributed.

His loss, at the peak of his activities and capacities, will be greatly felt by his many friends and colleagues, who extend their warmest sympathy to his family.

L. G. LAJTHA.

Ray Oliver died on March 5, 1976 following a relatively short illness due to a malignant cerebral tumour. As the person first responsible for his appointment in 1945 in medical physics and with whom he worked for most of his professional life until my resignation in 1970, I am eager to pay tribute to him both as a colleague, a scientist and a man. Having worked with him for 25 years, first at the London Hospital where he was deputy to L. A. W. Kemp and then at the Radiation Therapy Department in Oxford, I found him a staunch and loyal supporter with whom there were no personal difficulties. He was always helpful in discussion and prompt in action. As a scientist he did much especially in collaboration with Laszlo Lajtha and Eric Hall to further the development of radiobiology and medical physics as applied to radiotherapy. As a man he was honest and reliable, recognizing and generously fulfilling his obligations at all times to his immediate family, his family connections and his friends. I am grateful to have been associated with him so closely and, in visits to England during the first half of his illness, to have had the opportunity of appreciating the matter of fact courage with which he tackled his depressing situation. It is a pity that he did not have more time to make his impress as the Professor of Physics at the Royal Postgraduate Medical School to which he was appointed in 1971 and where he continued to fulfil his duties until a fortnight before he died. Others with more data readily available than I have here can write a more factual appreciation than I. I know he will be mourned and missed by many scientists and radiotherapists in all parts of the world as well as by his charming wife and two sons.

F. Ellis

May I add a few personal words to the many tributes already paid to Raymond Oliver? Like many physicists of my own and later generations, he was my teacher, my colleague and my friend. For nearly three years, in the late 1940s, Ray was my closest companion at The London Hospital and it was here that I observed in him those qualities that make for a good medical physicist: hard work, an agile and versatile mind, a sound knowledge of physics, ability to get on with people of all ranks and disciplines—and a lively sense of humour. These were qualities which Ray Oliver possessed in full measure and they served him well throughout his career.

After Ray left The London in 1950 our professional paths diverged for many years, but they converged again in the 1970s when we were both active in the British Institute of Radiology. Ray's work for the Institute was astonishing in its range and depth. Whether the subject matter was radioisotopes, radiation protection, radiobiology or whatever, if a report was needed to clarify some obscure or little-discussed topic—just ask Professor Oliver! and at the next meeting of the committee or group, there would be the report on the table: clear, concise and to the point. No one would have suspected that he had many other duties and obligations, as a Professor of Medical Physics and Head of an important hospital department. Yet everything was fitted in and completed, with apparent ease and calm.

Raymond Oliver will be sadly missed by all of us in radiology and in medical physics. Our deepest sympathies go to his widow, Lucy, and her two sons, Howard and David.

M. Cohen.

Dr. W. Hondius Boldingh

Willem Hondius Boldingh, who died in Eindhoven on January 28, 1976 at the age of 79, will be remembered as one of the leaders in X-ray apparatus design, not only in his own country, but throughout the world.

Hondius Boldingh joined the research laboratories of the Philips Company in Eindhoven as a young man, as an assistant to his famous predecessor, Professor Bouwers. Under Bouwers's leadership, Boldingh was introduced to the important advances of the 1920s in X-ray tube construction and, being a brilliant electrical engineer, he assisted and complemented Bouwers's work on the engineering side of high tension generators and control circuits.

Hondius Boldingh's original contributions included much work to automate the drudgery of free control of electrical parameters, whilst at the same time ensuring optimum results in radiography and safety of the X-ray tube by achieving full load conditions. He published many papers dealing with nomogram handling of radiographic controls, followed after the war by incorporating this in automatic circuitries which are nowadays called analogue computers but which in those days were termed "electrical nomograms". Close co-operation with Professor van der Plaats at the Maastricht Hospital—who had the somewhat arduous privilege of receiving the first prototype of all Hondius Boldingh's new machines, and of commenting upon them from the point of view of the radiologist—ensured a number of notable new developments in X-ray equipment.

I had the privilege, as Hondius Boldingh's counterpart at the British Philips, of working with him and I am proud to have counted him among my close friends. His brilliance, his scientific approach to all problems, his warm humanity and infectious humour and optimism made for a most harmonious relationship, not often found among colleagues in similar positions.

When Hondius Boldingh retired he characteristically pulled off a unique feat for a man of 65—he succeeded in obtaining a doctor's degree at Eindhoven University for his thesis on anti-scatter grids, which remains a valuable and compact reference book.

Hondius Boldingh left an indelible impression on most people with whom he worked, and he will be remembered as a most lovable character by all who knew him.

A. Nemet.

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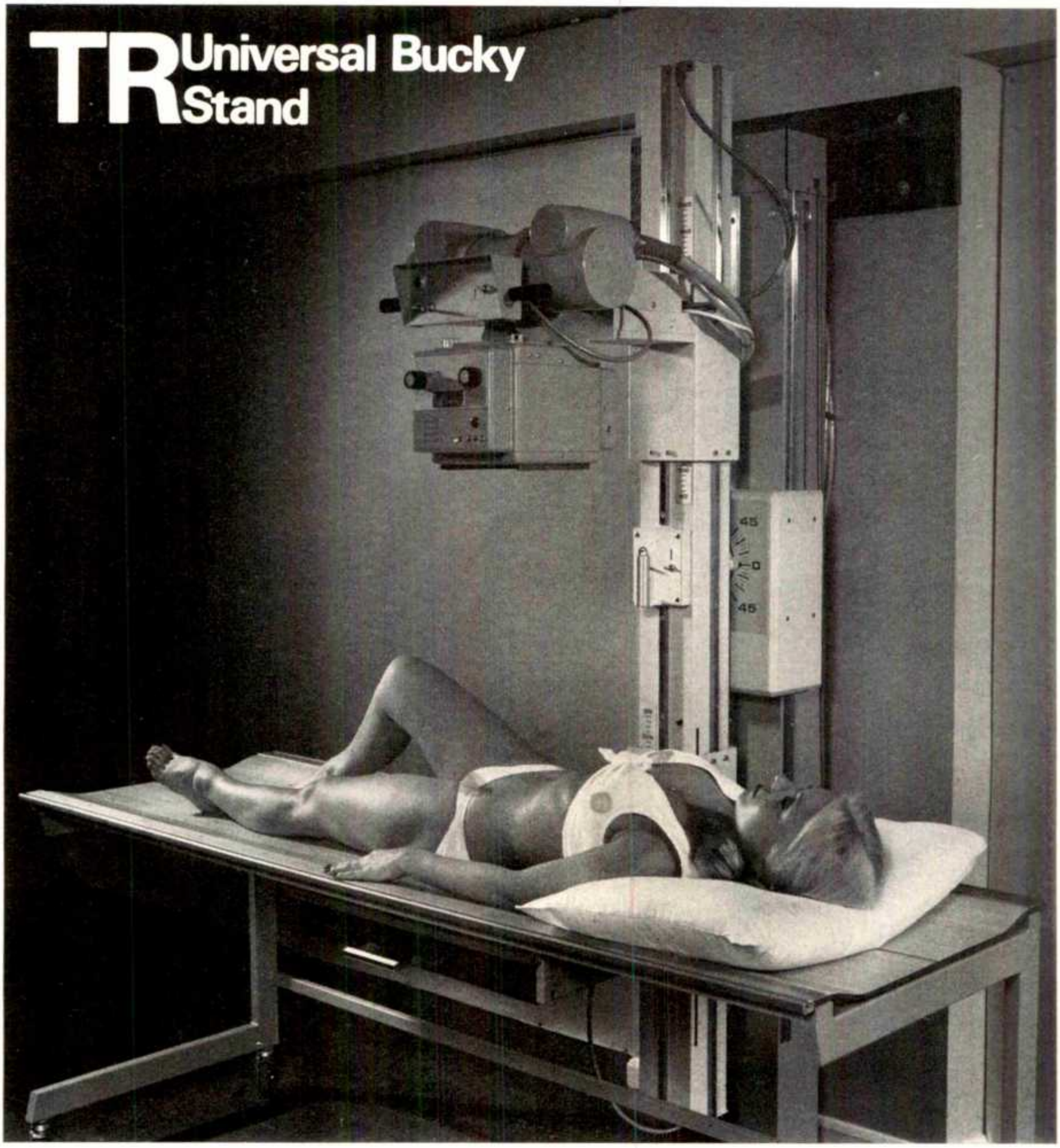

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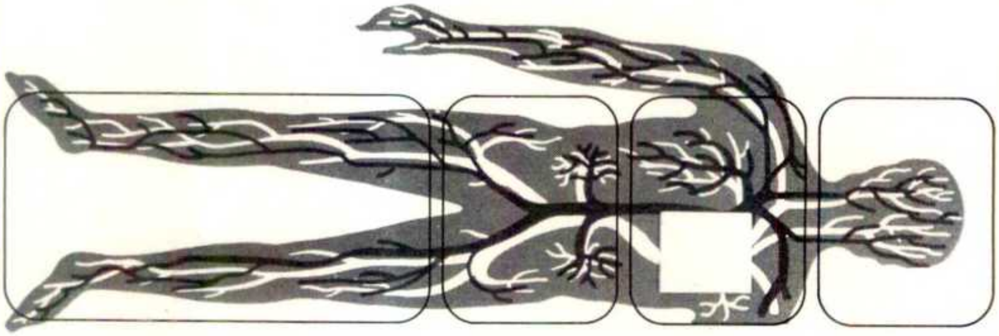

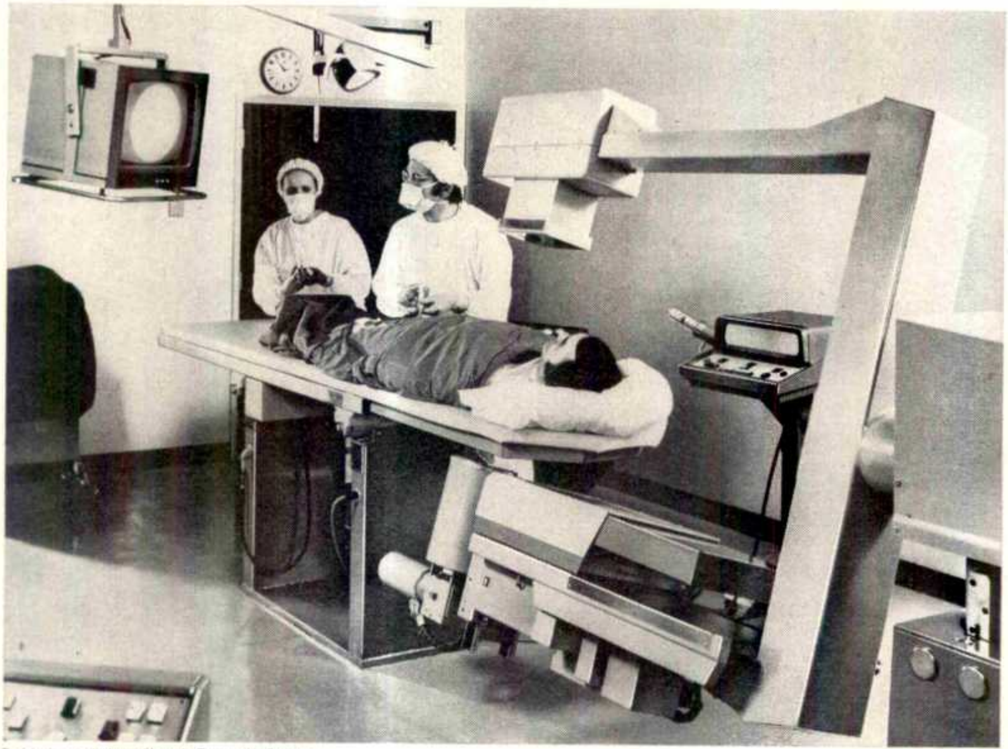

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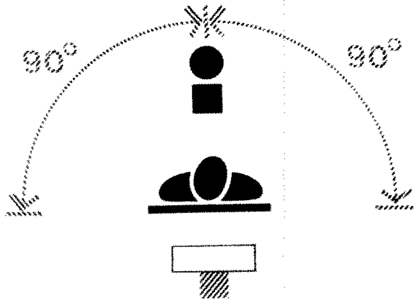

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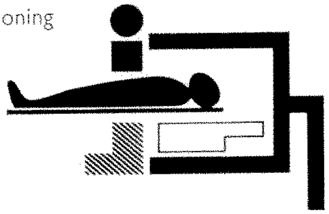

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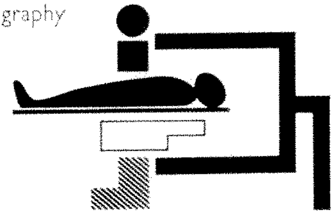

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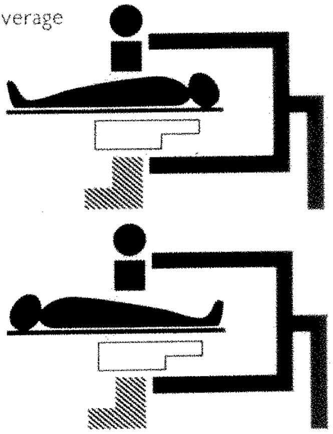

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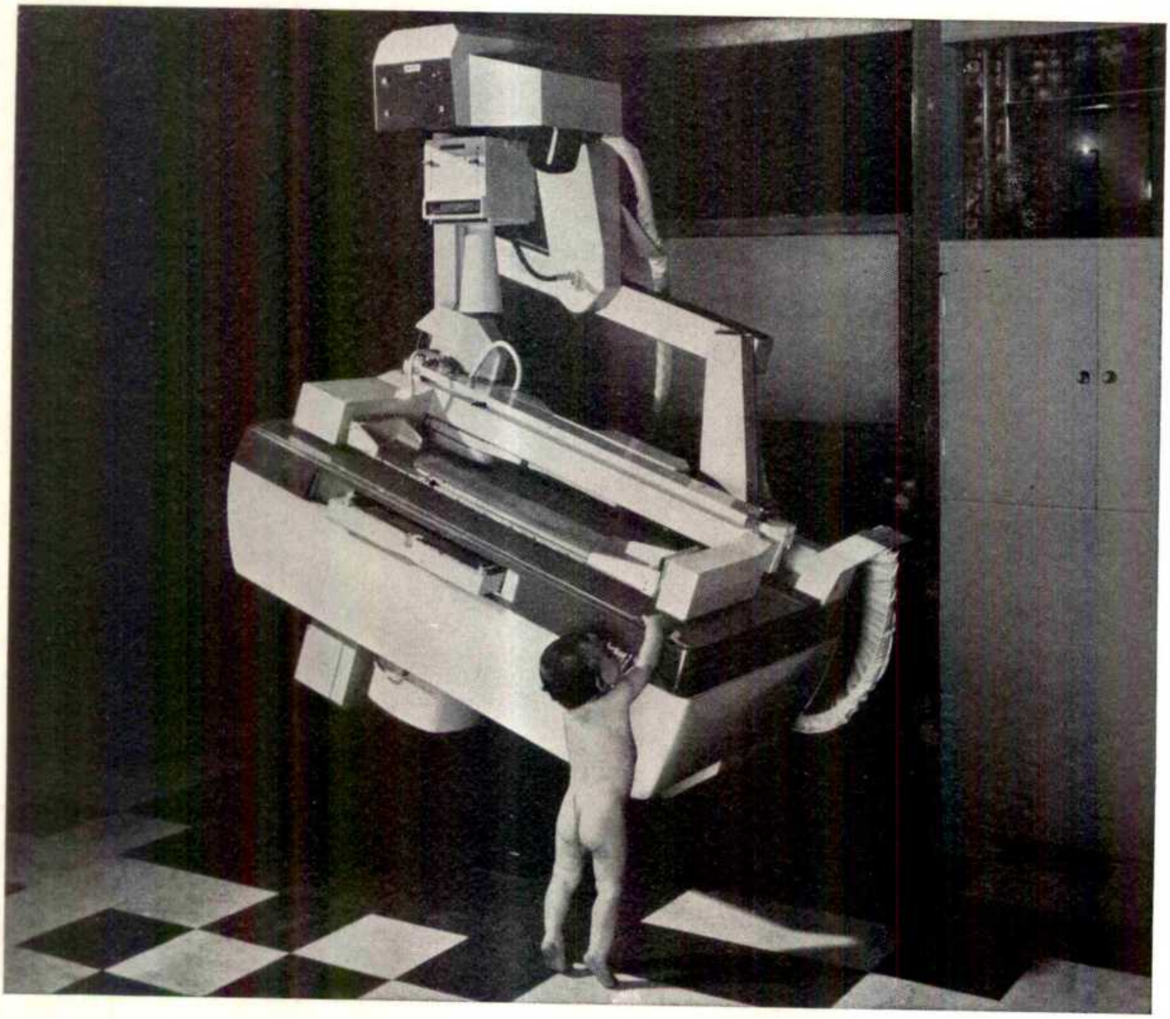

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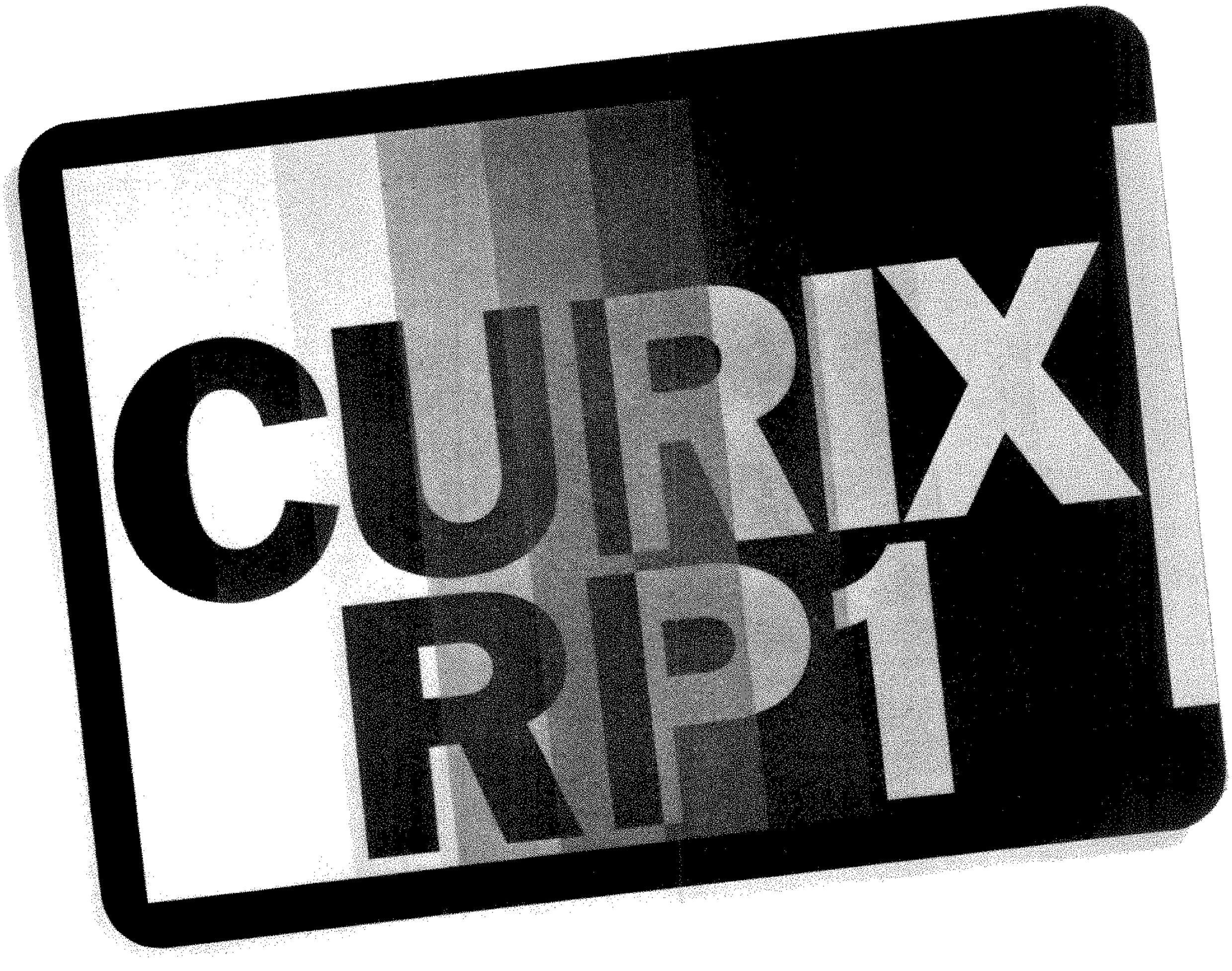

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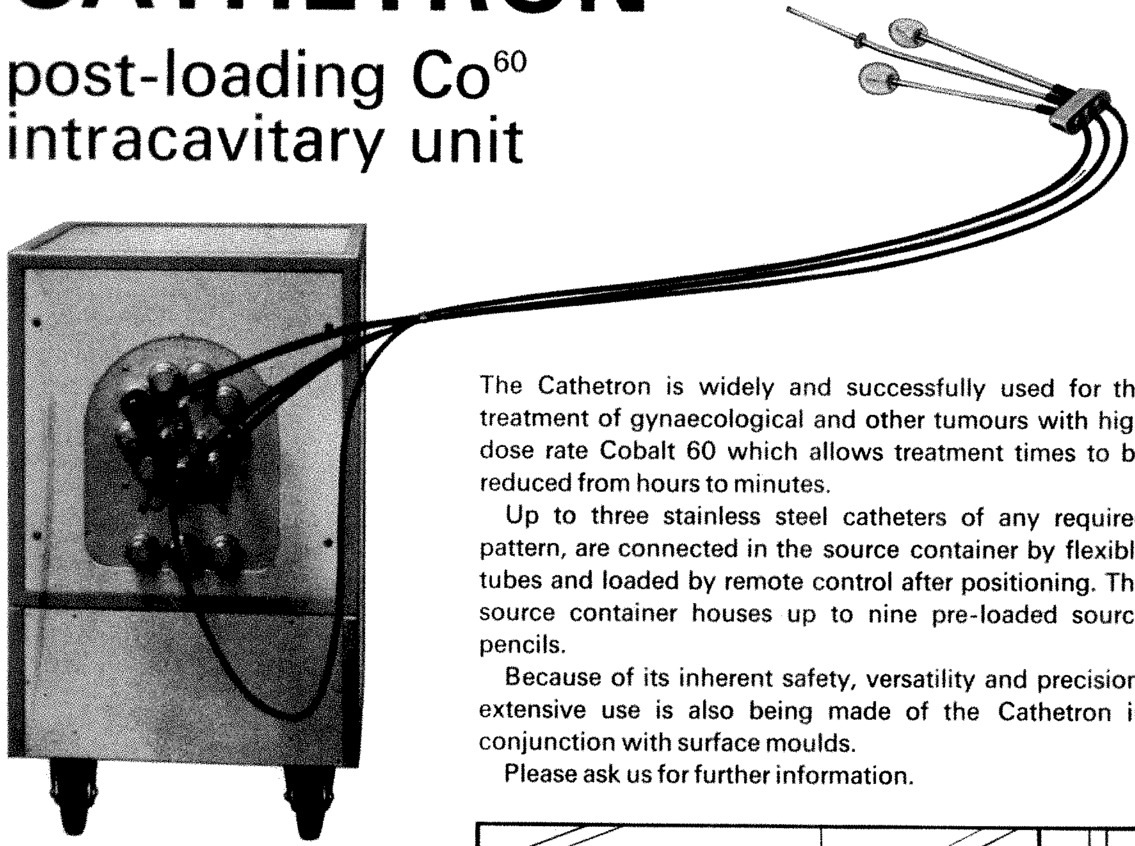

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REFERENCES

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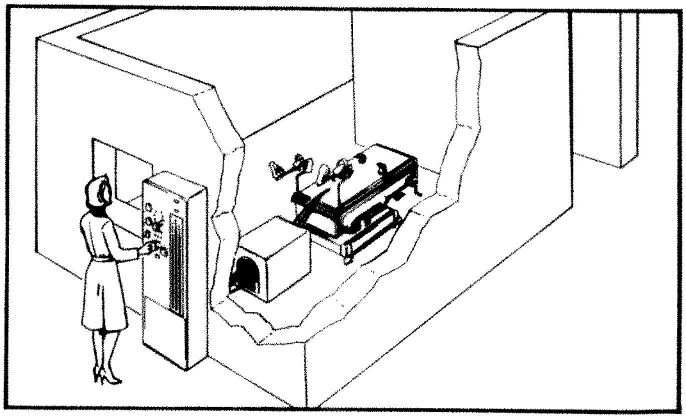

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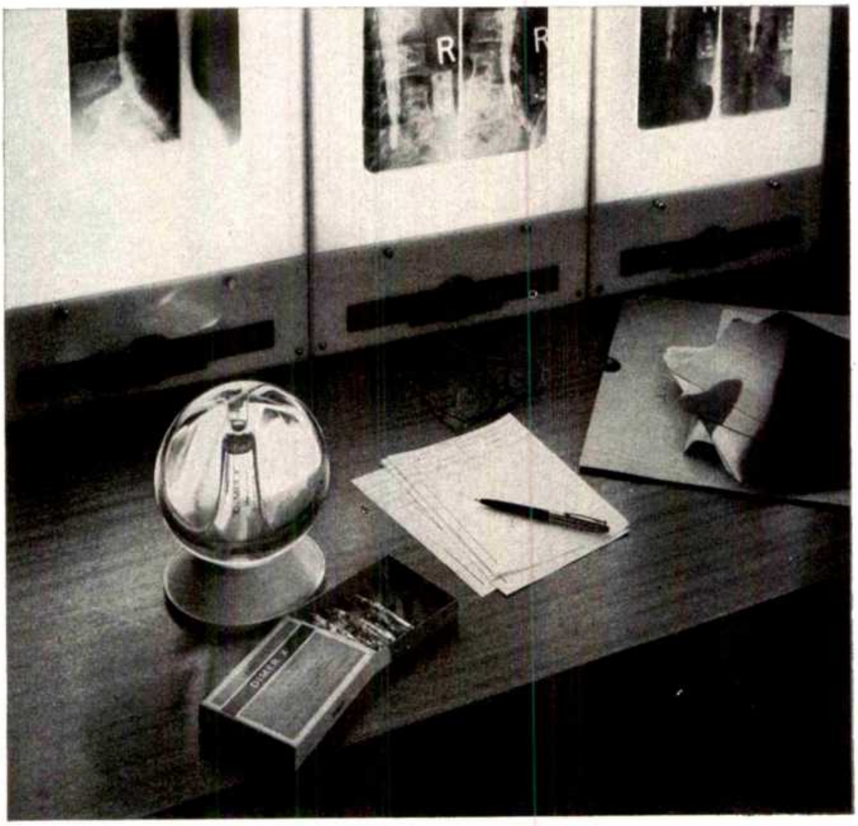

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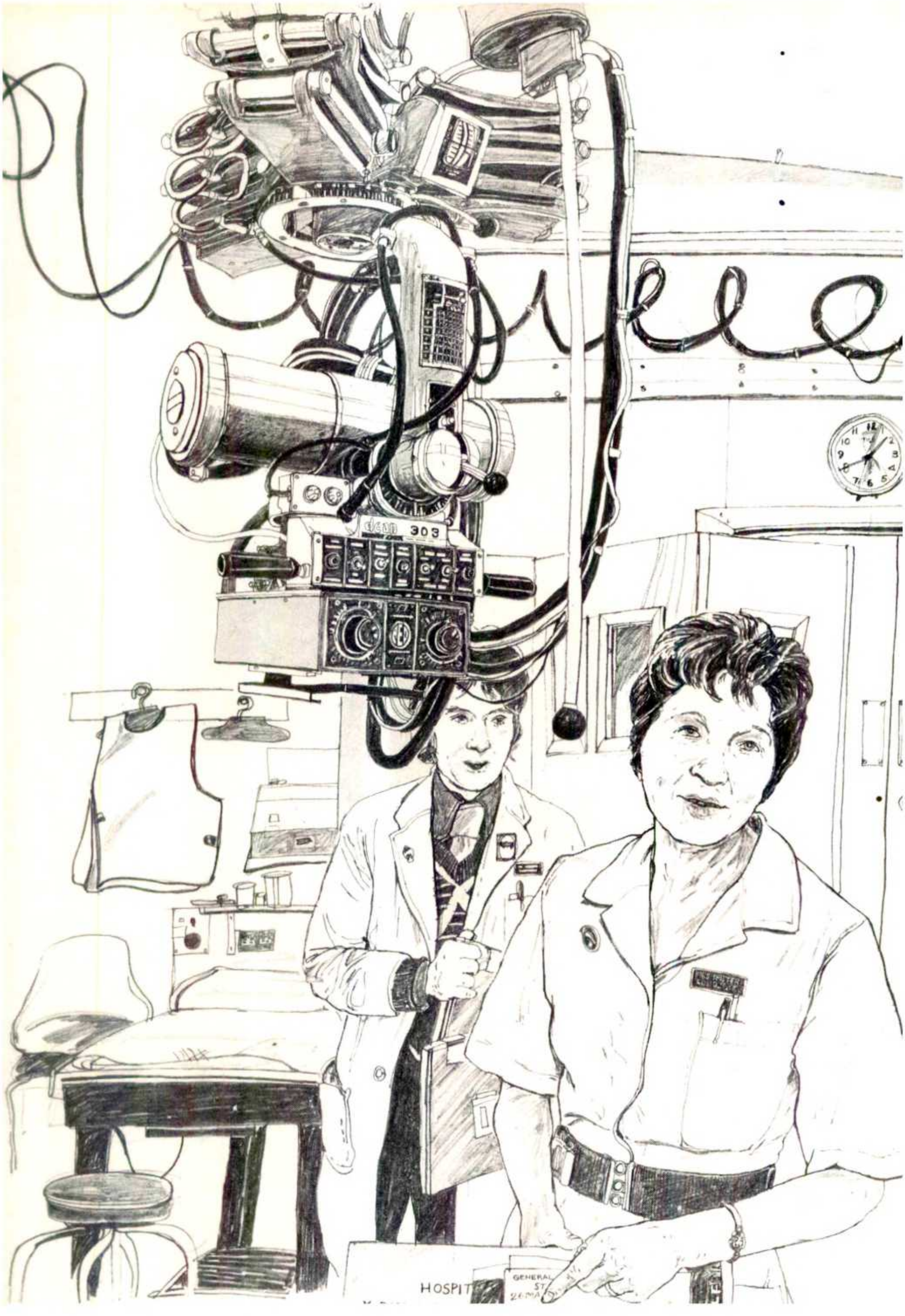
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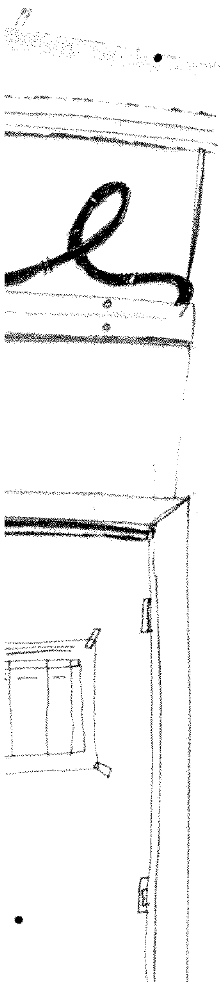

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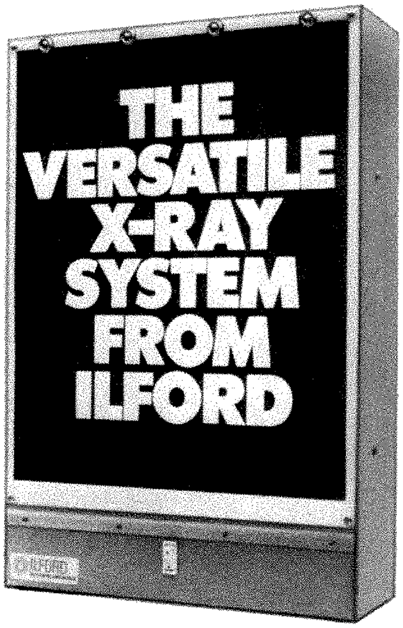

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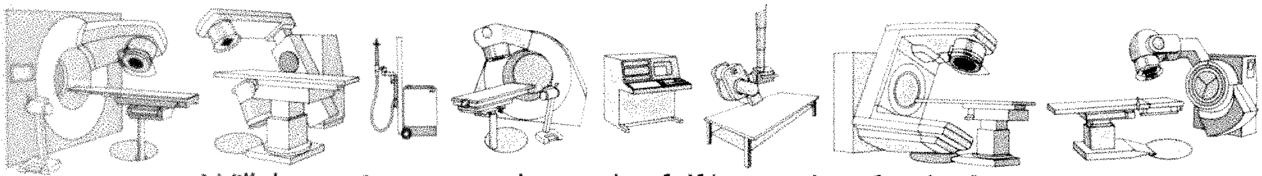

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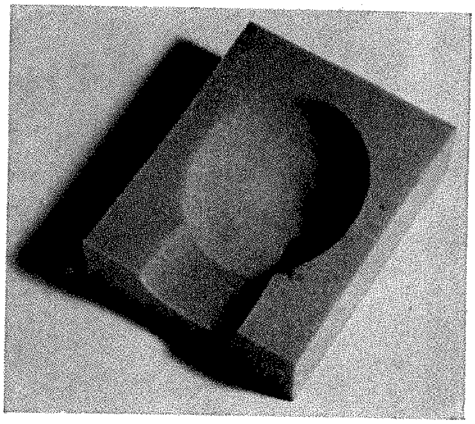

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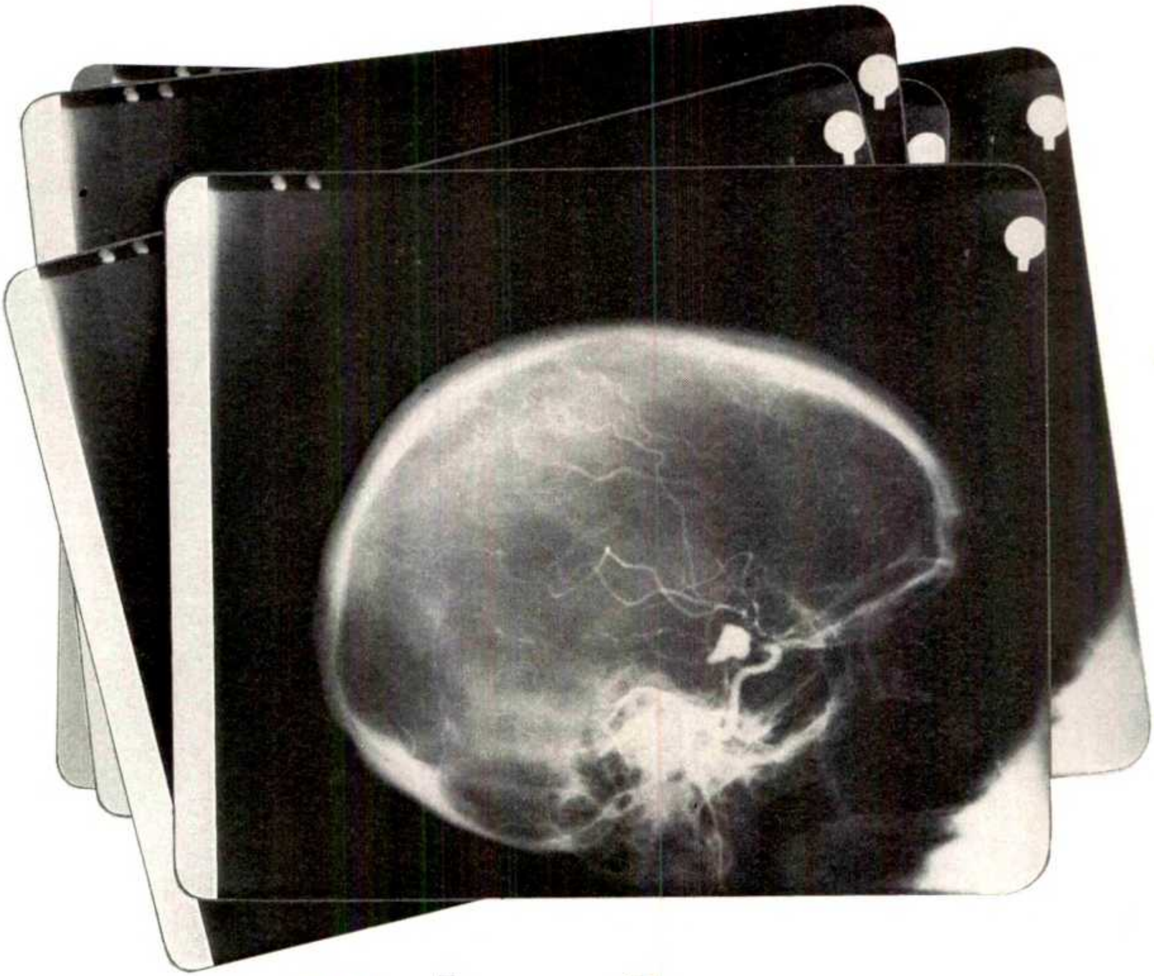

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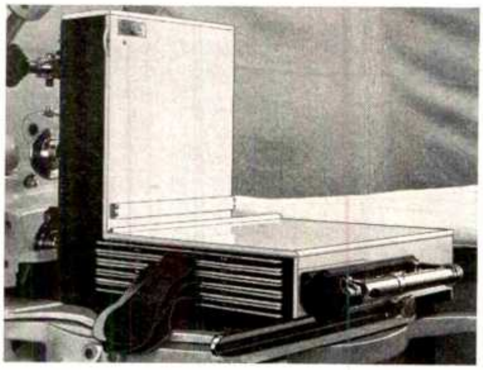

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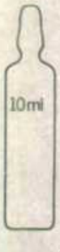

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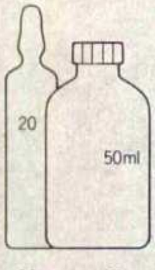

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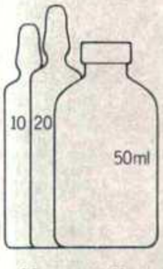

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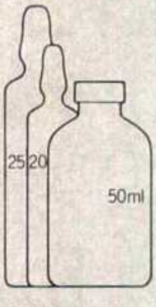

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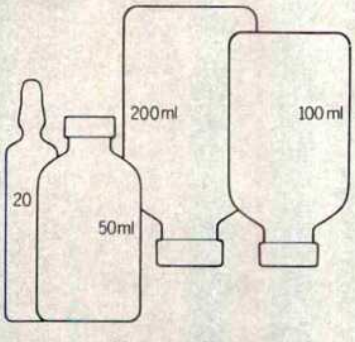

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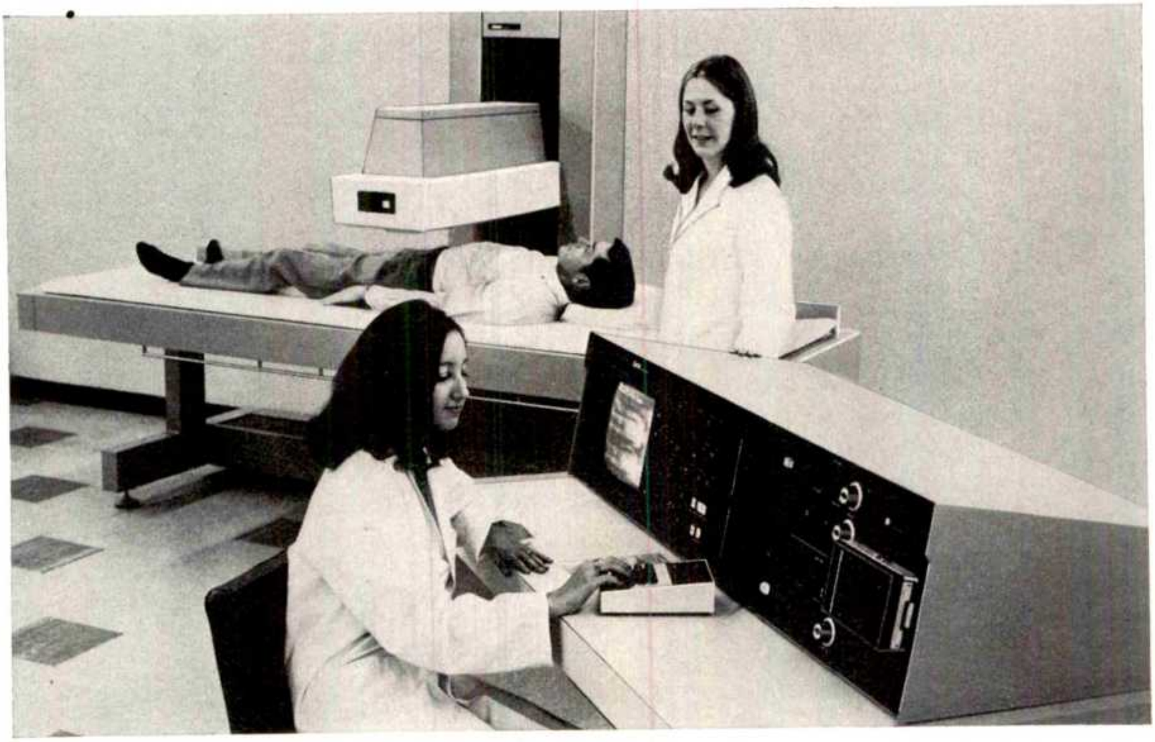

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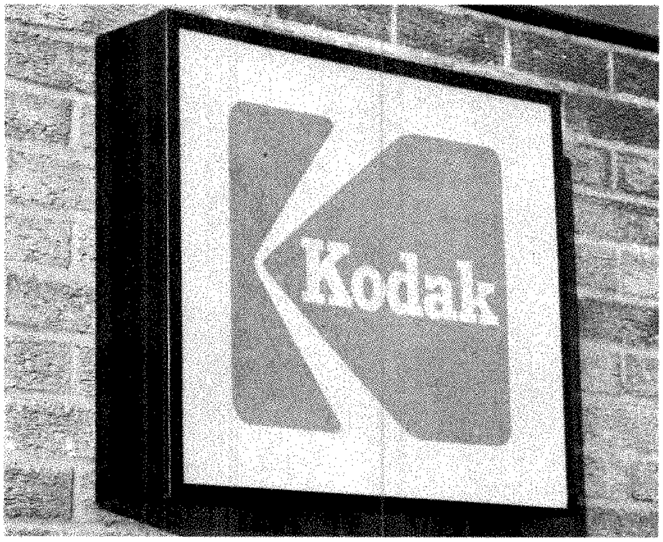

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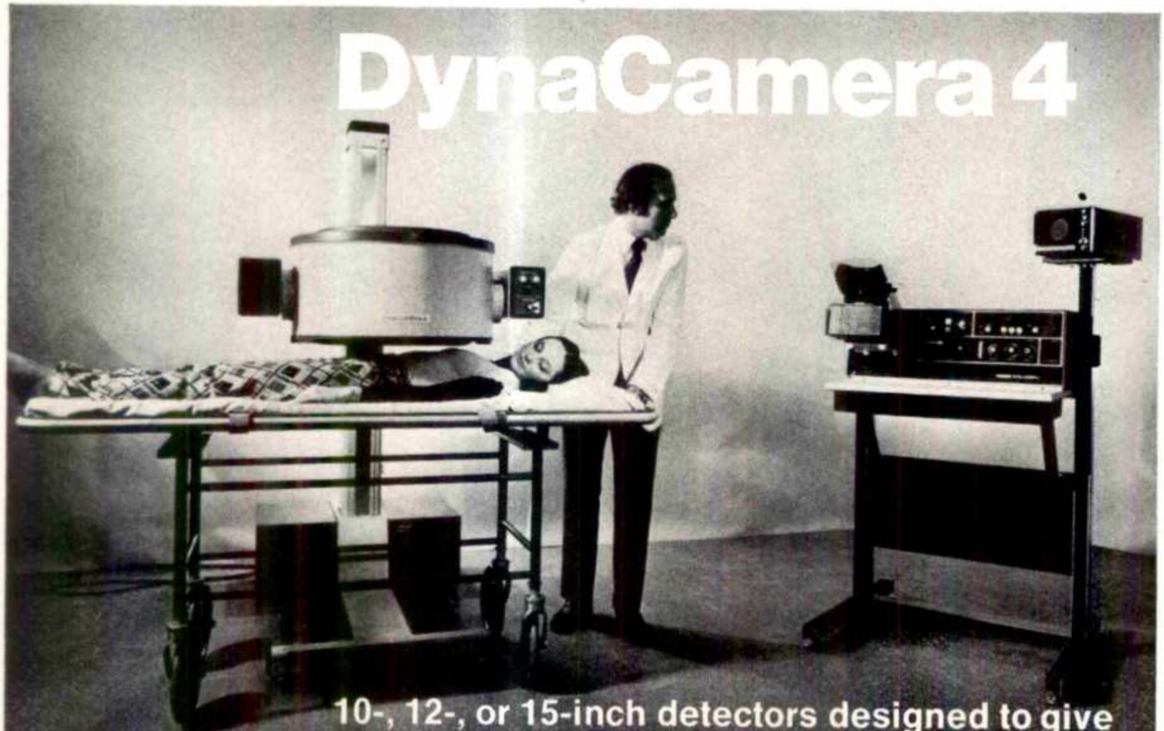

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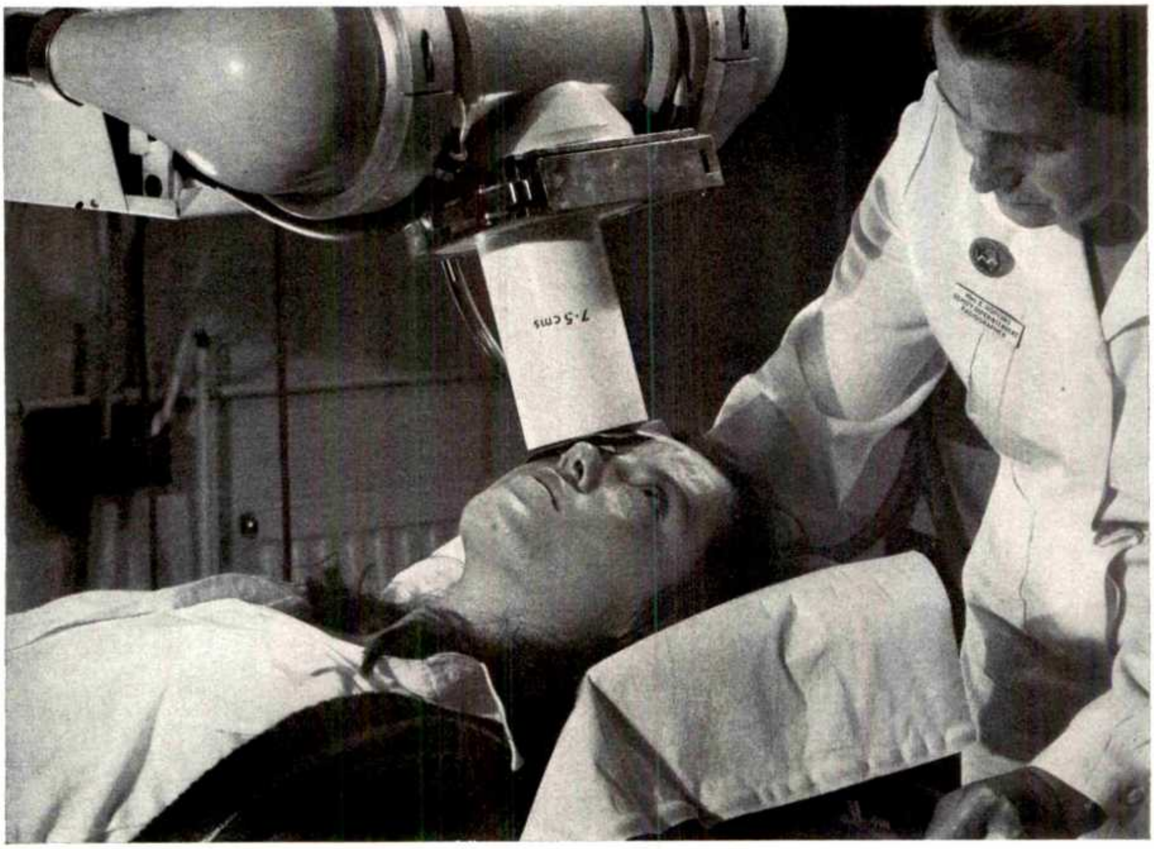

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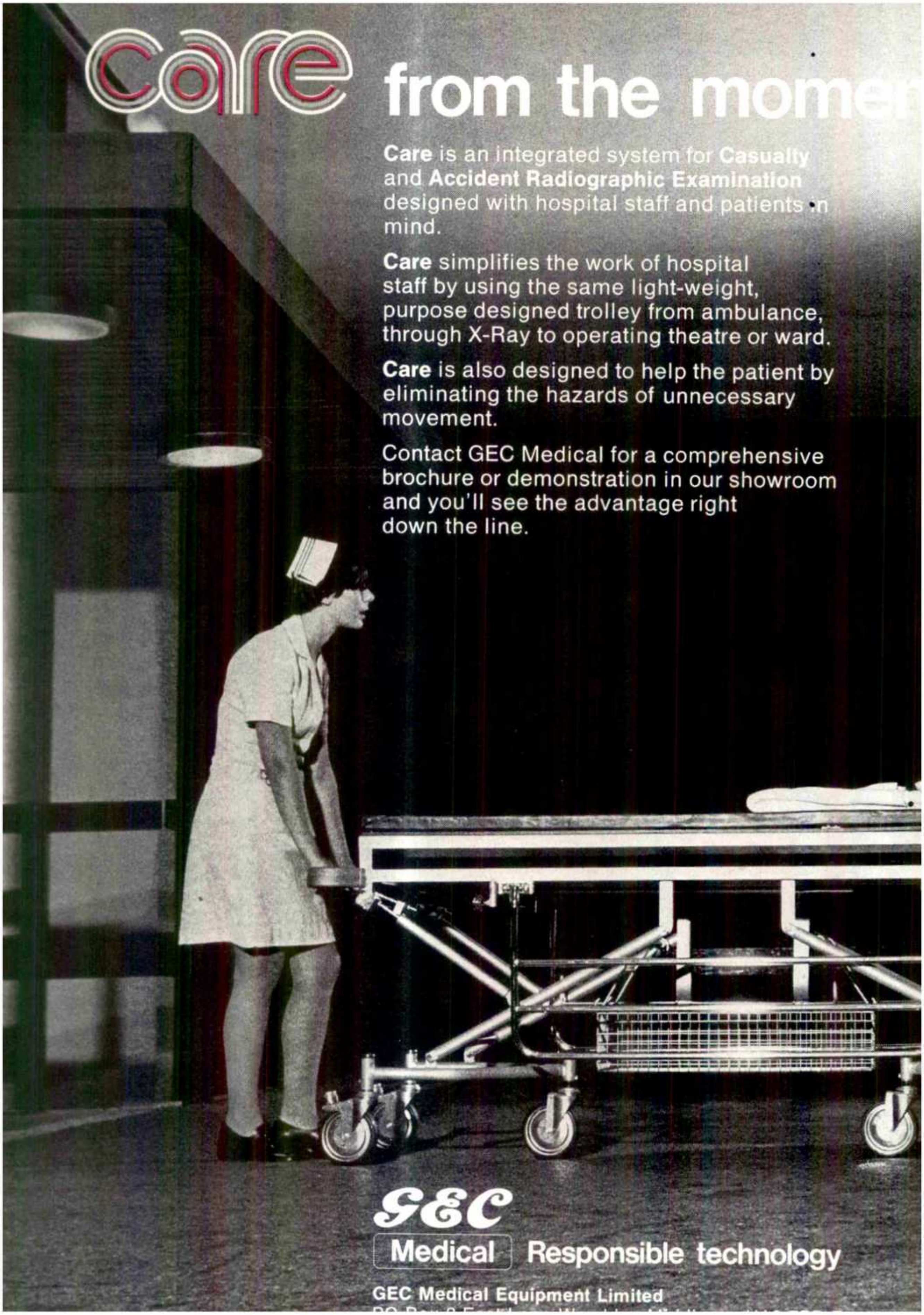

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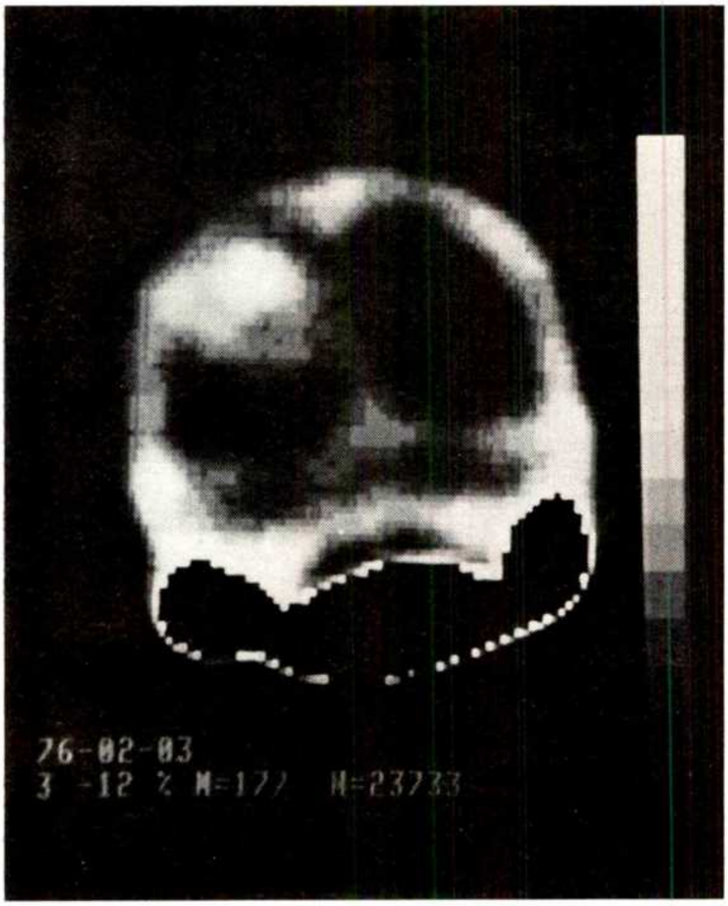

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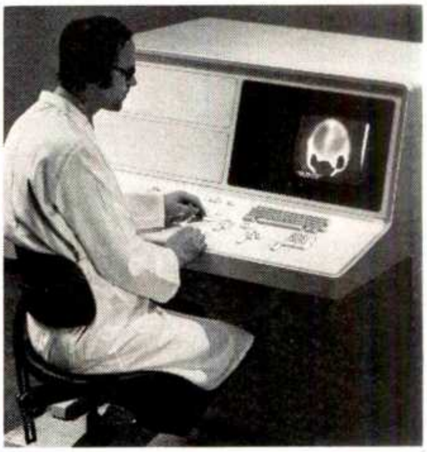

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Applications of Modern Technology in Radiotherapy

We are pleased to announce the publication of this report on treatment simulators. The report discusses the uses of simulators in radiotherapy and sets out guide-lines for their future development, both in the specifications of design parameters and in techniques for use. The specifications of simulators currently available from a number of manufacturers are tabulated and compared with those considered desirable by the authors.

The authors point out that the simulator has been a radiotherapy aid for a quarter of a century, but that to many its purpose and use are still undefined; they take the view that although verification is an important function of a treatment simulator, its main function is the accurate localization of the tissues in the region to be treated.

This Report is one of several now in preparation under the general title *Applications of Modern Technology in Radiotherapy.* The authors were brought together as a working group following discussions between members of The British Institute of Radiology, the former Faculty of Radiologists, the Hospital Physicists Association and The Society of Radiographers on the general need for information and guidance on the most effective ways of bringing new advances in technology into wide use in radiotherapy. We believe that this first report will prove of considerable interest to many present and prospective users of treatment simulators in Great Britain and in many other countries.

Members of the working group:

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Miss L. M. Craig, S.R.N., M.S.R.
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The British Journal of Radiology

Editorial

Letters to the Editor and quick publication of short communications

In October 1974, the Editors drew attention to the correspondence column of the journal, pointing out that it gave an opportunity for the airing of views on all kinds of topics and for quick publication of new results which could be described briefly and clearly. A further editorial in July 1975, invited readers' views on the question "must radiologists do all the reporting?"

We are pleased to see that these initiatives have produced a substantial increase in the number of letters submitted. Indeed, the number has increased so much that we now propose to divide the correspondence section into two parts: (a) true correspondence, being an airing of views on topical matters and comments on recently published papers, and (b) short communications, being reports of initial studies in new areas and comments which are too speculative or provocative for a normal paper. Speed of publication is essential for both of these new sections. We hope to reduce delays to a minimum by giving priority to both letters and short communications, and by keeping the normal vetting procedures to a minimum.

D. K. Bewley
F. Starer

1976, *British Journal of Radiology*, *49*, 658–659

Radiology now

Upper digestive tract radiology today*

The approach to the diagnosis of lesions in the upper digestive tract has changed since fibre-endoscopy hit the headlines, because a true assessment of the limitations of the standard barium meal became apparent for the first time since it was introduced over half a century ago. Before this there was insufficient criticism since surgery and autopsy were the only methods of judging our performance.

Reliance on the standard barium meal, and by that is meant a technique frequently using the normal fundal gas bubble to achieve some degree of double contrast, but without the deliberate addition of distending gas, has been called in question in numerous papers throughout the Western world. Classen in Germany, Cotton and others in Britain, Calenoff and Sparberg in the United States have independently stressed the disturbing level of inaccuracy inherent in this technique. The result was a swing heavily in favour of endoscopic diagnosis; a swing so far as to encourage some over-enthusiastic endoscopists to suggest that the patient actually preferred endoscopy to the barium meal!

What is our alternative? In 1958 Welin had shown the merit of double-contrast radiology of the colon, and Japanese radiologists, in close co-operation with their endoscopy colleagues and stimulated by the unenviable incidence of their particular form of gastric cancer, had turned to double contrast upper gastro-intestinal tract radiology in the early 1960s. In this country independent endoscopic assessments of double-contrast techniques are now coming into the picture and show a high degree of accuracy, well into the 90% level and rising as experience of the method grows. In short, false X-ray negative dyspepsia is rapidly becoming a thing of the past.

If we accept the situation as it now stands, and surely nobody can continue to swim against this tide for very long, the immediate effect is close co-operation between radiologist and endoscopist in place of the unfortunate separatism which tends to continue so long as the standard barium meal is practised. In my experience, up and down the country, endoscopists are only too pleased to be rid of the workload and boredom from an excessive number of false X-ray negative dyspeptics, allowing them to concentrate on their proper role as sophisticated trouble-shooters; a role in which the biopsy forceps makes a prior claim. Certainly the clinician in receipt of the routine double-contrast report shows his enthusiasm for this service and would not tolerate a return to the outmoded technique.

For the sake of argument, therefore, let us accept the undoubted value of double-contrast techniques. Some would then argue that this method should be reserved for the difficult diagnostic problem, and that the standard barium meal should continue as the initial routine survey. Surely this is inherently defeatist because the prime need is to get rid of false X-ray negative dyspepsia. The only sensible approach is to institute routine double-contrast radiology of the upper digestive tract in all departments.

Having said this, we must look at the implications of this decision. About one in every hundred of the population requires investigation for dyspepsia each year. This means a workload of 2000 examinations per 200 000 of the population, the average served by a district hospital. Here is the rub; super sophistication in each and every case, aimed at the demonstration of areae gastricae (the criteria laid down by Kreel and others (1973) as a "must" and necessitating drug-induced gastric atony) is not for the radiologist shouldering this sort of workload in normal hospital practice.

The technique adopted must therefore be simple, straightforward and easily learned by junior members of the department. It must be no more time-consuming than the conventional barium meal. I know a number of colleagues scattered over the country who practise simple double-contrast methods, using gas tablets or effervescent drinks according to their own choice and by their own experiment and initiative. These techniques, once standardized to individual choice, are easily turned to routine performance. Because there is no requirement to attempt a diagnosis whilst screening, with the detailed concentration and strain involved, the time taken to obtain the films for an overall contrast survey is certainly no longer than the time required for a conventional barium meal. Our own consultant and registrar experience is that this technique actually allows a more rapid turnover without risking loss of accuracy because of observer error. Surely the double-contrast method has a very real departmental advantage also. The diagnosis is made entirely from the films so that realistic consultation within the department is practical, and a library of lesions can be collected from which to teach the young radiologist, the clinician and the medical student.

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*Reprints from: Dr. W. G. Scott-Harden, Department of Radiology, Cumberland Infirmary, Carlisle CA2 7HY.

What of the medical student? In this department we are conscious that the students attached to our clinical colleagues actively seek a demonstration of gastro-intestinal contrast methods and the definition of lesions stemming from these. They express a significant interest. May this not be a recruiting potential for the future?

What of the young radiologist? Gastro-enterology has not generally been a favoured subject with the radiologist in training who tends to prefer the quasi-surgical activities embodied in the various forms of vascular radiology. Is this possibly because he is depressed by clinical criticism of the results of the conventional techniques and sees no dividend from his effort? This is a pity because clinical response to double-contrast accuracy is enthusiastic, and the dividend is very well worth while.

Double-contrast radiology and endoscopy are complementary, and when practised together in harmony, the diagnostic yield is lifted to 98%. It is also true that radiologists in training, who practise double-contrast methods, gain much by regular attendance at endoscopy sessions. Relating endoscopic appearances to radiological detail helps to unravel the mysteries of the "funny folds" which cause difficulty for those of us learning the trade.

Finally, the concept of the combined gastro-enterological clinic should be encouraged to the advantage of all concerned. This certainly enables the radiologist member to have a realistic clinical backcloth to his diagnostic problem and an influence in decisions regarding the choice and sequence of investigation. Inevitably his interest grows and his performance is enhanced.

Gastro-enterology practised in this way should then be a fascinating clinico-radiological subject. It is up to our teachers, both radiological and clinical, to encourage this approach to mutual advantage.

W. G. Scott-Harden

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Book reviews

Atlas of Enteroscopy. By L. Demling, M. Classen, and P. Frühmorgen, pp. 246, 1975 (Berlin, Springer-Verlag), $93.50.

Although entitled an Atlas, the first 69 pages of this book are devoted to a review of fibre optic instruments and accessories and descriptions of duodenoscopy, retrograde cholangio-pancreatography, jejuno-ileoscopy and colonoscopy. The text is clearly a translation from the original German, but suffers little for this. The remainder of the book has beautifully illustrated examples of normal and abnormal findings in the duodenum, small bowel and colon. It is lavishly illustrated with endoscopic photographs, pathological speciments and X-rays.

Although it is undoubtedly a useful reference work for practising endoscopists, the cost will unfortunately prohibit most gastroenterological departments from obtaining a copy of Professor Demling and colleagues' work.

R. Zeegen.

Ultrasonics in Medicine. Proceedings of the Second European Congress of Ultrasonics in Medicine, Munich, May 12–16, 1975. Edited by E. Kazner, M. de Vleiger, H. R. Müller, V. R. McCready, pp. 360, 1975 (Amsterdam, Excerpta Medica), $46.50.

The Second European Congress consisted of 230 proffered papers on all aspects of ultrasound. The proceedings were compiled before the congress on the basis of abstracts submitted and consists of 51 papers, often in slightly modified form, which represents a fair cross section of papers presented. The difficulties of judging a paper on the basis of a short abstract is reflected by the absence from the proceedings of several excellent presentations, but the book is nevertheless a valuable reference work and the 'subject index' is particularly useful. A list of papers read at the congress, but not included in the proceedings, would have increased the value of the book still further.

H. B. Meire.

1976, *British Journal of Radiology*, *49*, 660–664

The role of small bowel follow-through examination in the diagnosis of coeliac disease

By J. B. Masterson, M.B., M.R.C.P.I., D.M.R.D., F.R.C.R.,* and E. C. Sweeney, M.B., M.R.C.P.I., M.C. Path.†

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(*Received September, 1975 and in revised form November, 1975*)

ABSTRACT

A retrospective study of 105 barium follow-through examinations on 102 patients suspected of having malabsorption syndrome has been carried out to assess the usefulness of this technique in the diagnosis of coeliac disease. Comparison with histological and biochemical data has been made.

Of the 34 examinations on 31 patients with a proven diagnosis of coeliac disease, 30 examinations showed both abnormal X-ray and biopsy findings, two examinations showed normal X-ray appearance but abnormal jejunal biopsy and two showed normal jejunal histology but abnormal X-ray findings.

There were two cases with abnormal findings in which no gastro-intestinal cause could be found to account for the abnormality.

In view of the high sensitivity, non-invasive nature, ease and cheapness of the technique, barium follow-through examination is suggested as the initial investigation in patients suspected of coeliac disease.

RADIOLOGY IN ADULT COELIAC DISEASE

Since 1933 when Mackie first described the radiological changes in the small bowel in coeliac disease, many papers have been written, describing new signs, and attributing to certain signs varying degrees of specificity for the diagnosis of this disease.

Ruoff *et al.* (1968) stated that "the roentgen features in sprue are well established and highly specific . . .". Around the same time Sleisenger (1967) wrote "roentgenography of the small bowel gives findings that are characteristic but not specific" (of coeliac disease). In 1971 Kreel, writing on malabsorption, said . . . "the most important, if not the only function of radiology is to exclude an underlying anatomical abnormality, and not to try to compete with the biochemist". Has radiology then a part to play in the diagnosis of coeliac disease, or should it be reserved as Wharton (1974) suggests for "those cases where the jejunal morphology is shown to be normal but . . . there is good reason to incriminate gastro-intestinal disease"? In view of such conflicting opinion the present study was undertaken in an attempt to assess the value of the barium follow-through examination as a diagnostic procedure in coeliac disease.

SELECTION OF MATERIAL

A review of small bowel follow-through examinations, jejunal biopsy histology, and clinical data of patients who had jejunal biopsy performed in this hospital between 1967 and 1973 was carried out. The radiographs and biopsies were examined separately, and without prior knowledge of the patient's history and laboratory findings.

Of the 105 such studies performed on 102 patients in this period, the 34 studies on the 31 patients with a proven diagnosis of coeliac disease are the subject of this paper.

METHOD

A standard barium follow-through examination, of 300 ml. of Raybar non-flocculable barium was ingested by the patient and followed by fluoroscopy, with abdominal films taken at appropriate intervals until the barium had entered the colon. The peroral small bowel biopsies were obtained by Crosby capsule, under fluoroscopic control. Two biochemical criteria of malabsorption were recorded (a) faecal fat, and (b) urinary d-xylose excretion (Bockus, 1974; Dyer and Dawson, 1969).

Small-bowel radiographs were examined for evidence of the following signs:

(1) thickening of primary mucosal folds (Laws *et al.*, 1963);
(2) dilatation of the jejunal or ileal lumen (Laws *et al.*, 1963);
(3) segmentation/flocculation (Isbell *et al.*, 1969);
(4) transient intussusception (Ruoff *et al.*, 1968);
(5) prolonged transit time (Isbell *et al.*, 1969);
(6) moulage (segments of proximal jejunum in sprue in which the folds are smooth and appear to be completely effaced) (Kantor, 1939; Adlersberg *et al.*, 1954;
(7) thickening of duodenal mucosal folds (Nicolette and Tully, 1971);
(8) decreased number of duodenal mucosal folds (*ibid.*);

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(9) asymmetry of duodenal mucosal folds (*ibid.*);
(10) duodenal dilatation (*ibid.*).

RESULTS

1. Two patients had normal X-ray appearances but showed partial villous atrophy on jejunal histology.
2. Two patients showed abnormal X-ray appearances but had normal jejunal histology. One was a treated case of coeliac disease, with abnormal d-xylose excretion, the other showed partial villous atrophy on jejunal biopsy 18 months later, and a similar X-ray appearance.
3. In 30 examinations, both X-ray and biopsy findings were abnormal (Fig. 1).
4. Twenty-five patients had faecal fat estimation and of these 17 (68 per cent) showed steatorrhoea. Thirty-one patients had d-xylose excretion tests and 26 (83·7 per cent) showed decreased urinary excretion (Fig. 1).
5. The distribution of abnormal radiological signs is described in Table I.
6. The final diagnosis in a group of 19 patients with abnormal small bowel follow-through examinations due to diseases other than coeliac disease is outlined in Table II.

DISCUSSION

The diagnosis of coeliac disease is often difficult. So protean are its presentations, that it must be considered in the differential diagnosis of a very large number of conditions (Barry *et al.*, 1974).

How then is the clinician to set about confirming or refuting his suspicion that a patient is suffering from this disease? No single investigation will detect an abnormality in all cases. In an assessment of the role of d-xylose excretion test in detection of coeliac disease, Sladen *et al.* (1973) found that the test was in error in 20–40 per cent of cases. Our experience in this study supports the view that this test "yields little guidance for diagnosis or therapy", 16 per cent of our cases having a normal d-xylose excretion test.

Gent and Creamer (1968) found that 25 per cent of their patients with coeliac disease did not have steatorrhoea. 32 per cent of the patients in the present series did not have steatorrhoea (Fig. 1).

Both small bowel follow-through examination and jejunal biopsy detected abnormality in 95 per cent of cases in this series, each having two false-negative results.

Four patients, of the 103 studied, showed abnormalities on follow-through examination, but extensive investigation (in one case including laparotomy), failed to reveal any other abnormality. In

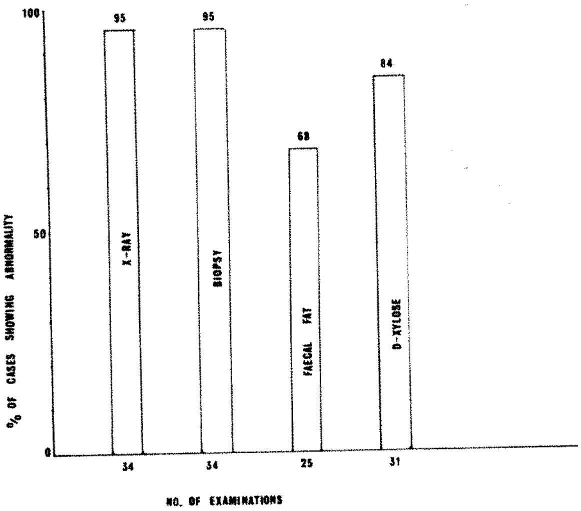

Fig. 1.

Showing the percentages of each of the four parameters (jejunal histology, small bowel follow-through examination, faecal fat, and urinary d-xylose excretion) which were abnormal, in patients with coeliac disease.

TABLE I

THE DISTRIBUTION OF ABNORMAL RADIOLOGICAL SIGNS IN 34 BARIUM FOLLOW-THROUGH EXAMINATIONS ON 31 PATIENTS WITH COELIAC DISEASE

Dilatation of bowel lumen	88%
Segmentation/flocculation	65%
Thickened mucosal folds	88%
Transient intussusception	15%
Moulage	3%
Prolonged transit time	9%
Dilatation of duodenum	36%
Thickened duodenal folds	72%
Asymmetry of duodenal folds	45%
Sparse duodenal folds	50%

TABLE II

FINAL DIAGNOSIS IN 19 PATIENTS SHOWING ABNORMAL SMALL BOWEL FOLLOW-THROUGH EXAMINATION DUE TO DISEASES OTHER THAN COELIAC DISEASE

Gastric surgery with small bowel bacterial contamination	3 patients
Atrophic gastritis with small bowel bacterial contamination	5 patients
Diabetic enteropathy	5 patients
Crohn's disease	1 patient
Lymphoma involving small bowel	2 patients
Tropical sprue	1 patient
Whipplés disease	1 patient
Chronic pancreatitis	1 patient

two of these cases a diagnosis of irritable bowel syndrome (Kalser *et al.*, 1956) was made, and in the other two judgement was reserved to await further follow-up studies.

That two patients with coeliac disease, both of whom showed partial villous atrophy on jejunal biopsy, had normal barium follow-through examinations, demonstrates the fact that a small number of patients with coeliac disease will not be detected by this technique. This has been reported previously by Laws *et al.* (1963) and Isbell *et al.* (1969).

THE RADIOLOGICAL SIGNS

Of the radiological signs used in this study, all except one (transient intussusception) appeared to be entirely non-specific, occurring in similar percentages of patients with coeliac disease and in the 19 patients with other diseases of the small bowel (Fig. 2). Transient intussusception appears to be relatively specific for coeliac disease and tropical sprue (Isbell *et al.*, 1969; Cortell *et al.*, 1967), and in this series was only seen in those two conditions. It was seen in six patients, five who had coeliac disease and one who had tropical sprue. One of the cases in this series with coeliac disease was found at laparotomy to have several easily reducible intussusceptions of the small bowel. The only other condition in which this sign has been reported is one case of giardiasis in the series of Isbell *et al.*, 1969.

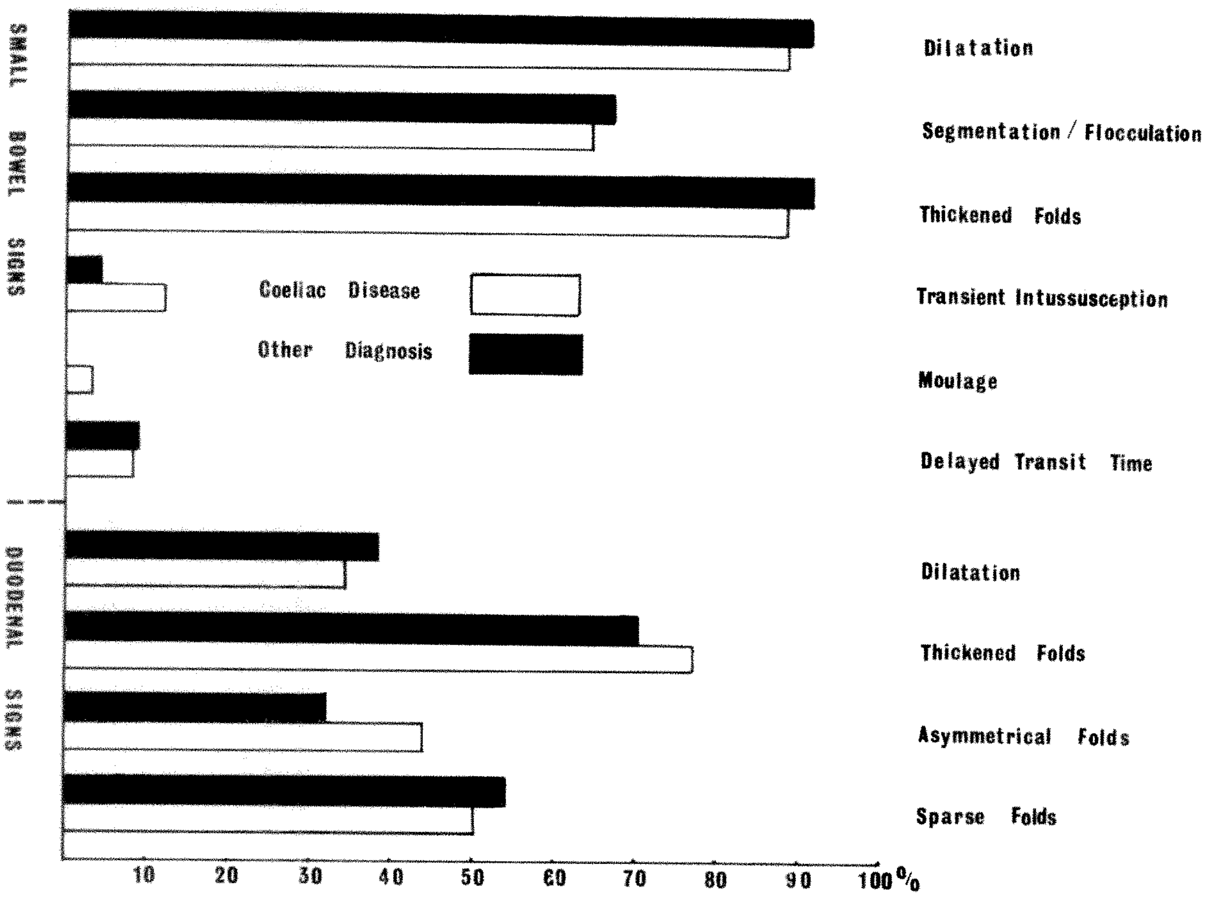

FIGURE 2

FIG. 2.

Comparison of incidence of radiological signs in patients with coeliac disease and in patients with miscellaneous small bowel disease.

The abnormal radiological signs most frequently found in the small bowel in coeliac disease were dilatation of the bowel lumen and thickening of mucosal folds, both occurring in 88 per cent of cases (Table I). Thickening of duodenal mucosal folds was seen in 72 per cent of patients with coeliac disease in whom suitable films were available.

Changes of segmentation/flocculation were present in 65 per cent of cases of coeliac disease.

Moulage was not found to be a useful sign in our experience, chiefly due to lack of a satisfactory definition of the sign as distinct from dilatation of bowel lumen with flattening of mucosal folds. It was difficult to decide at what point these signs constituted a separate entity of moulage.

Delayed transit time was not a frequent finding in this series, and this has been the experience of other authors (Isbell *et al.*, 1969). The normal range of transit time is so wide (Kim *et al.*, 1968) as to make this sign almost meaningless. Three cases of coeliac disease showed delayed transit time. Duodenal changes as described by Nicolette *et al.* (1971) were found in all cases of coeliac disease in this series in whom suitable films were available, but were also found in cases of every other diagnosis in the patients with small bowel abnormality other than coeliac disease. These signs we consider to be a useful adjunct to the signs in the small bowel, but as with all signs except transient intussusception, they are non-specific. It is of some importance to note that duodenal signs were extremely useful in two cases where the small bowel abnormality was minimal, and this fact should be borne in mind in the positioning of the tube tip in the performance of a small bowel enema. If the tip is placed in the jejunum, these signs may not be elicited.

Conclusion

Whilst jejunal biopsy is an invasive technique,

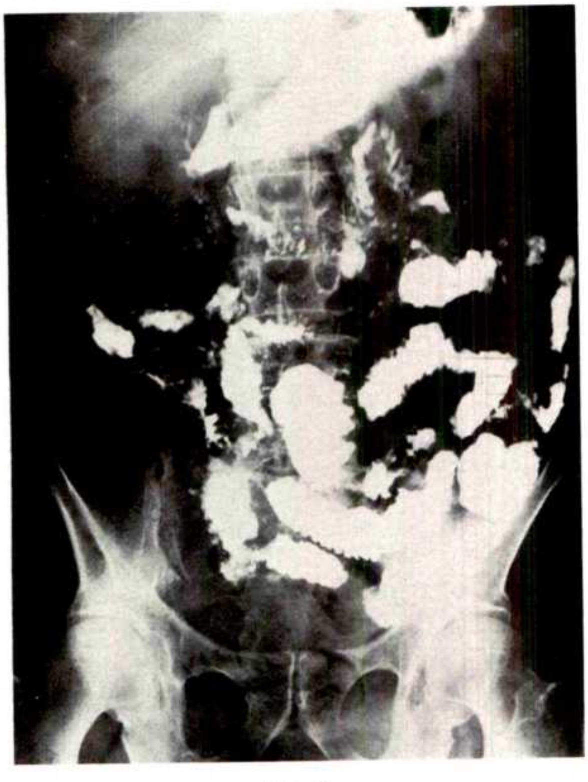

Fig. 3.

Barium follow-through examination showing segmentation of the barium column with widening of the bowel lumen and thickening of the mucosal folds.

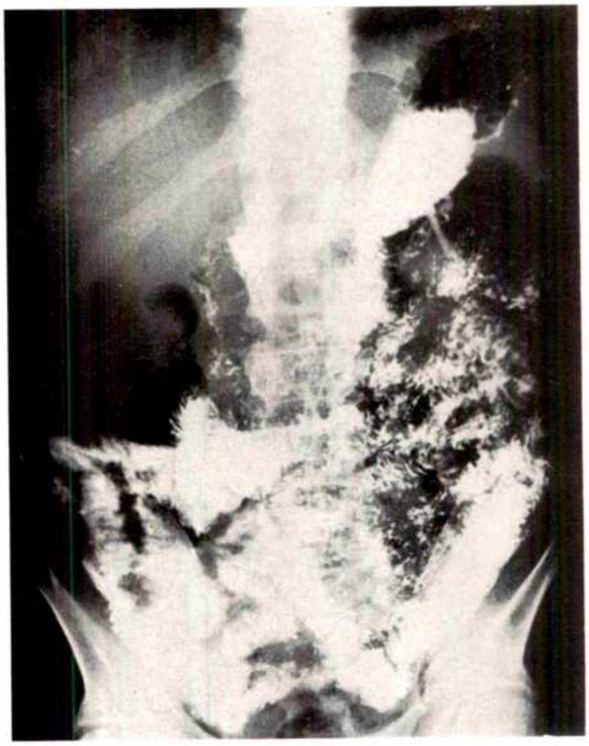

Fig. 4.

Barium follow-through examination showing flocculation and coarsening of mucosal pattern.

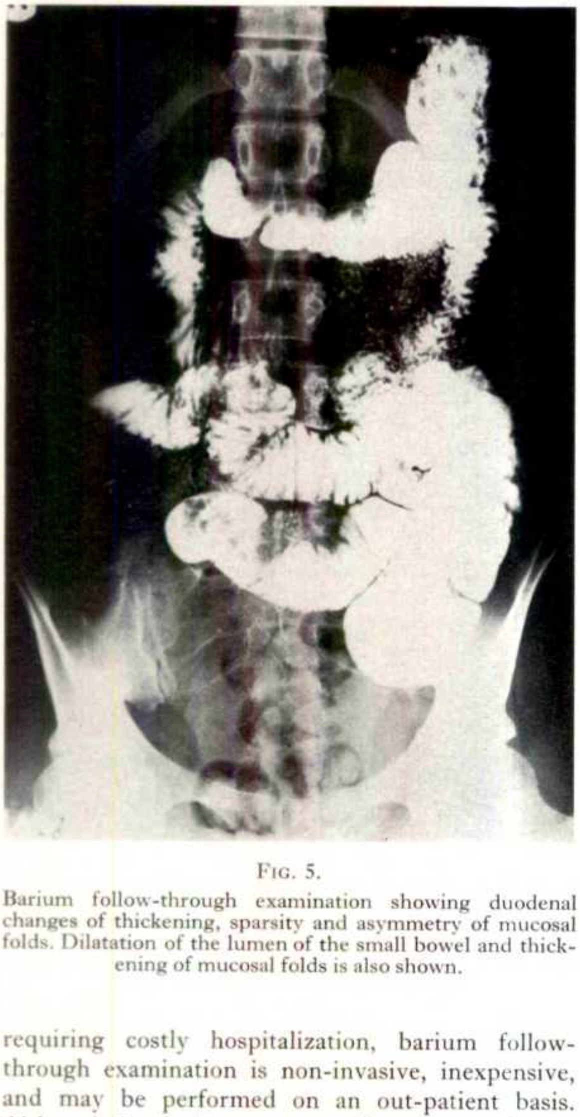

FIG. 5.

Barium follow-through examination showing duodenal changes of thickening, sparsity and asymmetry of mucosal folds. Dilatation of the lumen of the small bowel and thickening of mucosal folds is also shown.

requiring costly hospitalization, barium follow-through examination is non-invasive, inexpensive, and may be performed on an out-patient basis. Although its findings are usually non-specific, its high sensitivity in detecting small bowel abnormality in coeliac disease (equal to that of jejunal biopsy), its potential for revealing alternative causes of malabsorption, together with the cheapness and simplicity of the technique, recommend it as the initial investigation of patients suspected of having coeliac disease.

The subsequent development of partial villous atrophy in a patient whose original biopsy was normal, although his follow-through examination at that time was abnormal, indicates that radiological changes may precede biopsy changes in some cases of coeliac disease, and that repeat biopsy should be obtained in such cases.

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The accuracy of radiological and computer diagnoses in small bowel examinations in children

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ABSTRACT

A prospective study has been made of the accuracy of the diagnoses made by radiologists and by two computer methods of prediction in 120 children having radiological examinations of the small bowel. The predicted diagnoses were calculated using the Bayesian and Relative Likelihood techniques. The results have been compared with the final clinical diagnoses, which have been considered to be "correct".

It was found that in 94 (78 per cent) children with no small-bowel disease the correct diagnosis was made by the radiologist in 79 (84 per cent), by the Bayesian method in 86 (91 per cent) and by the Relative Likelihood method in 77 (82 per cent) children. In the 26 (22 per cent) children with small-bowel disease the correct diagnosis was made by the radiologist in 21 (81 per cent), by the Bayesian method in 13 (50 per cent), and by the Relative Likelihood method in 11 (42 per cent) children.

The accuracy of the three methods of interpretation of signs has been compared using the diagnostic test rating index, which takes into account the false-positive and false-negative results, as well as the correct and incorrect results. The radiologist rating was 0·76, the Bayesian method 0·57 and the Relative Likelihood method 0·51. The index for the radiologist was significantly greater than that for the Relative Likelihood method ($p < 0{\cdot}05$).

Computer predictions are based on observations made by the radiologist and may be affected by the initial selection of signs, the compression of information into a "normal" or "abnormal" format, and the size of the bank of information available. They offer an objective test of the significance of selected radiological signs. Computer diagnosis provides a useful research tool, but in this study was less accurate than the radiologist.

Computers were first applied to the problems of diagnosis in patients with congenital heart disease (Warner *et al.*, 1961), and since then have been used as an aid in the differential diagnosis of a number of diseases (Ross, 1972). Most reports have been concerned with the separation of diseased patients into different diagnostic groups, indicating that a considerable amount of preliminary sorting has already taken place, whilst in medicine the first problem often is to decide whether or not a recognizable disease is present. The common methods of predicting the diagnosis in a new patient are based on calculating probabilities and the Relative Likelihood method and Bayes' Theorem are two techniques of doing this. The Relative Likelihood method compares the signs in a particular patient with the frequency with which they occur in previous patients known to have had the disease and predicts the probability of each named disease being present. Bayes' Theorem uses the same method of prediction, modified by the known incidence of disease in the population previously studied (Lusted, 1968).

Computer-aided diagnosis using Bayes' Theorem is claimed to increase the accuracy of clinicians in the diagnosis of abdominal pain (de Dombal *et al.*, 1975). Bayes' Theorem was less accurate than Relative Likelihood in separating diseases of the thyroid (Boyle *et al.*, 1966), but the two methods showed much the same accuracy in differentiating liver diseases (Fraser, 1971). In the gastro-intestinal tract the differences between benign and malignant gastric ulcers have been assessed and then used in a Bayesian programme to predict the diagnosis in 14 new patients (Wilson *et al.*, 1965). The incidence of disease and selected abnormal signs in children having radiological examinations of the small bowel has been determined (Jeans, 1972), and this information has now been used as the basis for a prospective study. This study compares the accuracy of radiologists' interpretation of radiographic signs with that of computer-predicted diagnoses based on the same signs using the Relative Likelihood and Bayes' methods in identifying patients needing further investigation.

MATERIAL AND METHODS

A prospective study was made of 120 consecutive small-bowel examinations performed at the Bristol Royal Hospital for Sick Children using a standard technique (Bradfield and Chrispin, 1965). The indications for examination included clinical suspicion of coeliac disease, failure to thrive, dwarfism and unexplained anaemia or abdominal pain.

The presence or absence of radiographic signs and the radiological diagnosis were recorded routinely by the radiologist responsible for each examination at the time of reporting, and later transferred to punched cards. A computer program written by the authors based on published formulae (Lusted, 1968) used the incidence of signs and diseases previously found in 100 children with a known diagnosis (Table I) to predict the diagnosis for each new patient (Table II). Subsequently the clinical records were examined to discover the final clinical

TABLE I

Percentage incidence of signs and disease in 100 patients previously examined, and used to predict the diagnosis in new patients

Radiological signs	Coeliac disease	Other diseases	No small bowel disease
1. Increased bowel width for age	73%	50%	13%
2. Transit time of 2½ hours or more	73%	29%	29%
3. Flocculation seen in two or more films	99%	29%	13%
4. Dilution of column of barium	27%	7%	11%
5. Absence of mucosal pattern or presence of transverse folds	99%	36%	7%
6. Easy visual separation of loops of bowel	91%	57%	36%
Numbers of patients	11	14	75

TABLE II

Three examples of the computer print-out for diagnoses calculated by Bayes' Theorem

Diseases in order of probability			
	Order	Disease	Probability
Case No. 103	1 2 3	Normal Other Coeliac	0·99 0·06 <0·01
Case No. 112	1 2 3	Coeliac Other Normal	0·91 0·29 0·02
Case No. 120	1 2 3	Normal Coeliac Other	0·25 0·23 0·16

TABLE III

Comparison of clinical diagnosis with results of three methods of interpretation of radiological signs. The numbers in italics are those in whom the diagnoses agreed

	Clinical diagnosis			
	Coeliac disease	Other small bowel disease	No small bowel disease	Total
Radiological diagnosis				
Coeliac and ? coeliac disease	*16*	3	14	33
Other small bowel disease	0	*5*	1	6
No small bowel disease	2	0	*79*	81
Total agreed diagnoses				*100* (83%)
Bayesian diagnosis				
Coeliac and ? coeliac disease	*12*	4	7	23
Other small bowel disease	0	*1*	1	2
No small bowel disease	6	3	*86*	95
Total agreed diagnoses				*99* (82%)
Likelihood diagnosis				
Coelic and ? coeliac disease	*9*	3	13	25
Other small bowel disease	4	*2*	4	10
No small bowel disease	5	3	*77*	85
Total agreed diagnoses				*88* (73%)
Total patients with clinical diagnosis in group	18 (15%)	8 (7%)	94 (78%)	120 (100%)

diagnosis which was based on the results of all investigations including jejunal biopsy when indicated, and clinical progress.

Three main groups of diagnoses were found. In 94 (78 per cent) children no small-bowel disease was found. In 18 (15 per cent) children coeliac disease was present, and in the remaining eight (7 per cent) children there were other small bowel abnormalities including fibrocystic disease, intestinal lymphangiectasis, and abnormalities following repair of tracheo-oesophageal fistulae and methotrexate therapy for leukaemia. Radiological diagnoses have been combined into the same three groups and both definite and possible cases of coeliac disease have been combined into the coeliac group since the purpose of radiological examination is to separate patients without small bowel disease from those needing further investigation. Computer results were considered to diagnose no small bowel disease when "normal" had the highest value on the list and was at least 0·05 greater than the value of the next diagnosis (Case 103, Table II). Patients were considered to have coeliac disease if this was highest on the list (Case 112, Table II), if this diagnosis was within 0·05 of the highest value, or if no disease had a value of more than 0·6 (Case 120, Table II). All other patients were considered to have "other small bowel disease". These criteria were chosen to ensure that patients in whom the diagnosis was not definitely either of normality or disease would receive further investigation.

Results

There was agreement between the radiological diagnosis and the final clinical diagnosis in 79 (84 per cent) children with no small bowel disease, in 16 (89 per cent) children with coeliac disease, and in five (65 per cent) of the eight children with other small bowel diseases (Table III). The Bayesian diagnosis agreed with the final clinical diagnosis in 86 (91 per cent) children with no small-bowel disease, in 12 (33 per cent) children with coeliac disease, and in one (13 per cent) child with another small bowel disease. The Relative Likelihood diagnosis agreed with the final clinical diagnosis in 77 (82 per cent) of the children with no small-bowel disease, in nine (50 per cent) of those with coeliac disease, and in two (26 per cent) of those with other diseases.

False negative diagnoses were made in two (8 per cent) of the 26 children with small-bowel disease by the radiologist, in nine (35 per cent) by the Bayesian diagnosis and in eight (31 per cent) by the Relative Likelihood method (Table IV). In the 18 patients with coeliac disease two (11 per cent) were reported as normal by the radiologist, six (33 per cent) were predicted to be normal by the Bayesian method, and nine (50 per cent) normal by the Relative Likelihood method.

False-positive diagnoses were made in 15 (16 per cent) of the 94 patients with no small-bowel disease by the radiologist, in eight (9 per cent) by the Bayesian method, and in 17 (18 per cent) by the Relative Likelihood method. In the 102 patients who did not have coeliac disease, probable coeliac disease was diagnosed by the radiologist in 17 (17 per cent) children, by the Bayesian method in 11 (11 per cent) and by the Relative Likelihood method in 16 (16 per cent) children.

TABLE IV

Percentage error rate of three methods of diagnosis

	Clinical diagnosis	
	Coeliac disease	All small-bowel disease (including coeliac)
Radiologist		
False negative	11%	8%
False positive	17%	16%
Bayesian diagnosis		
False negative	33%	35%
False positive	11%	9%
Likelihood diagnosis		
False negative	50%	31%
False positive	16%	18%

The index for rating diagnostic tests described by Youden (1950), in which the true and false-positive and negative diagnoses are combined, has been used to compare the accuracy of the three methods in identifying possible small-bowel disease. The value of the index is one if the diagnostic test is always correct, and 0 if it does not distinguish between healthy and diseased patients. The calculated value is 0·76 for the radiological diagnoses. 0·57 for the Bayesian diagnoses, and 0·51 for the Relative Likelihood diagnoses. The only significant difference is that between the radiological and Relative Likelihood diagnoses ($p<0{\cdot}05$).

Discussion

The introduction of computers into the field of medical diagnosis was expected to increase the accuracy of diagnosis (Ledley and Lusted, 1959), but no major advantage has yet appeared. The accuracy of radiological diagnosis has been of interest since it was found that there was a considerable variation in the reading of chest radiographs, both by different observers and by the same observers on different occasions (Yerushalmy, 1969). In the diagnosis of small bowel disease clinical impressions and biochemical results, radiological and histological interpretations all have their error rates and all contribute to the final clinical diagnosis against which their accuracy has to be judged (Buck and Gart, 1966). Although the histological appearance of subtotal villous atrophy is the hallmark of coeliac disease, the same appearances can be caused by milk intolerance (Roy-Chaudhury *et al.*, 1966) and normal histology can be seen when gluten intolerance is present (Visakarpi and Immonen, 1967). It is impractical to subject all children with possible small-bowel disease to biopsy so that the accuracy of radiology in separating children with disease from those without is of importance.

The expression of an error rate as a percentage may be misleading since this ignores the importance of assessing the false-negative and false-positive errors. In this study the overall percentage of agreed diagnoses for radiological and Bayesian diagnoses is 83 per cent and 82 per cent respectively, giving the impression that they have a similar degree of accuracy. Youden's method (1950) of combining the false-positive and false-negative results with the correct and incorrect diagnoses into a composite index provides a numerical assessment of the overall usefulness of a test, and allows comparisons between different studies. This index shows that the radiological diagnoses were significantly more accurate than those made by the Relative Likelihood method and more accurate than the Bayesian method. There are a number of possible reasons for this result.

The computer predictions are based on the observations made by the radiologist. When reporting the examination the radiologist was required to look for the possible presence of each selected sign in every case in an attempt to diminish errors of observation. Errors in radiology may occur through faults in technique, observation, interpretation or communication, and this study has assessed the variation in interpretation of signs, since the same signs were available to the radiologist and the two computer programs. The signs used were examined in the preliminary survey and selected as being independent of each other. The correlated factors of age and bowel width were combined into one sign, and factors like the sex of the child which are not relevant were excluded. The frequency of appearance of each sign in different groups of patients provides an automatic weighting in the computer calculations so that some signs are more valuable than others. However, the simplification of the information into the "normal" or "abnormal" form may withhold some information from the computer that was available to the radiologist.

The radiologist has access to information given on the request form by the clinician that is not available to the computer. This information may be misleading since it often justifies the request for examination by suggesting that disease is present. This may influence the radiologist, and partly account for his higher false-positive diagnosis rate. It also appeared that any abnormal sign was reported by the radiologist as indicating the possible presence of disease, whilst the computer calculations produced a low probability value unless several signs were present.

The size of the bank of information will affect the accuracy of prediction. The 11 cases of coeliac disease in the bank allowed the diagnosis to be made correctly by the Bayesian method in two-thirds of the new patients but was less successful using the Relative Likelihood method. This last method is thought to diagnose rare diseases with more accuracy (Ross, 1972) since the frequency of occurrence of the disease is not taken into account, but this has not been confirmed in the study. Adding the first 50 proven cases to the bank in our study did not affect the diagnosis in the succeeding 70 patients, because the incidence of small-bowel disease in the children was small, and it would be necessary to have a much larger bank to provide a significant increase in information about diseased patients.

CONCLUSIONS

The use of a computer to make diagnoses from selected radiological signs with no other information provides an objective test of the significance of the signs, and has shown that the radiological signs used enable the majority of children with small-bowel disease to be separated from those without. Assessment of results by considering the percentage of correct diagnoses is misleading. When assessed by the diagnostic test rating index the diagnoses made by the radiologists were significantly more accurate than those predicted by the Relative Likelihood method, and were also more accurate than those predicted using the Bayesian method. It is probable that the benefits of attempting computer diagnosis are in enforcing the preliminary assessment of the importance of particular signs in making a diagnosis and then in providing an objective test of this assessment. The use of this technique will probably remain a useful research tool rather than a practical aid in day-to-day diagnosis.

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We are grateful to the clinicians of the Royal Hospital for Sick Children, Bristol, for referring their patients for examination and for allowing us access to patients' records. We are also grateful to the radiologists who reported the examinations, to our colleagues for their helpful criticism, and to Dr. I. R. S. Gordon and Professor J. H. Middlemiss for their encouragement.

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Book reviews

Assessment of Skeletal Maturity and Prediction of Adult Height (TW2 Method). by J. M. Tanner, R. H. Whitehouse, W. A. Marshall, M. J. R. Healy, and H. Goldstein, pp. vii + 99, 1975 (London, Academic Press) £9·00.

It is probable that there is overuse of radiological assessment of bone age in paediatric practice; nevertheless, its determination does have an important place, especially in relation to endocrinological problems and growth disorders. The most widely used method is a comparison of a radiograph of the hand and wrist with the standard pictures in the well-known atlas of Greulich and Pyle.

In 1962, Tanner *et al.* produced a new system, believed to be more flexible and derived from a more solid mathematical basis; the present book describes a revised version of this which they call the TW2 method. Selected bones of the hand and wrist are individually classified into one of eight or nine stages, each of which carries a score value (according to sex and mathematical significance). This score is added up and the equivalent bone age read from a table. Three types of score are possible "RUS" is the score derived from 13 centres—the lower epiphyses of the radius and ulna and those of 11 of the short bones of the hand; the "carpal score" is obtained from seven of the carpals and the "20-bone TW2" is derived from all 20 of these sites. The bone age can be read from any one of the three scores. The RUS bone age can be used to calculate a predicted adult height from the child's present height, chronological age and a series of coefficients.

For each ossification centre and carpal bone, there are radiographs, diagrams and descriptions at each stage of maturity. In practice, the reviewer felt that the diagrams and radiographs are generally more useful than the descriptions in selecting the correct stage; some of the radiographs are too dark in their printing. Adding up the scores, with totals in three or four figures, is tedious even with a calculator. The whole process is decidedly slower in application than the Greulich and Pyle method.

Estimation from a selection of available radiographs showed some variation in the three types of scoring. A normal boy of 11 years had bone ages of 10·5, 11·2 and 13·2 whereas the Greulich and Pyle bone age was 11 years. In general, however, there was better agreement than this. A boy of 10 with renal failure had a Greulich and Pyle rating of 7 to 8 years and TW2 figures of 7·9, 8·0, and 8·2. The most difficult part of the assessment is allocating the stages of the phalanges of the thumb.

This appears to be a method that will have restricted application; the Greulich and Pyle approach of matching pictures is quicker and easier to apply, forming a standard that is accurate enough for practical clinical purposes. The reviewer cannot see that TW2 will replace it except possibly for specialist research purposes. In some ways it is a pity that at least part of the energy expended on developing the new system was not devoted to an updated atlas resembling that of Greulich and Pyle.

R. ASTLEY.

Current Concepts in the Diagnosis and Treatment of the Intra Abdominal Cancers, Edited by R. J. Cohen, J. R. Castro and M. S. Krier, pp. xiv+276, 1975 (Flushing, U.S.A. Medical Examination Publishing Co. Inc.) $15.00.

The proceedings of the San Francisco Cancer Symposium of 1974 are reported in this small volume. Papers on the diagnosis and treatment of intra-abdominal cancer are presented and discussed by a group of well-known American experts of different disciplines.

Although there is nothing very new in this book and the discussion tends to wander from the subject, it gives a well-balanced picture of the present situation.

There is an excellent contribution by Dr. Vincent DeVita Jr. on 'Trends in the Therapy of Ovarian Cancer' which includes sensible suggestions for future prospective clinical trials.

In a paper on 'The role of Surgery in Gynaecological Cancer', Prof. John McLean Morris expresses openly his concern for the escalating financial cost to patients of some of the modern diagnostic and therapeutic methods. A good deal of what he has to say is controversial, but his good sense, open mindedness and concern for the quality of life of his patients make this a most refreshing section.

This is not a book for every library shelf but those who treat intra-abdominal malignant disease will find it of interest.

THELMA D. BATES.

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Azygography in the pre-treatment evaluation of oesophageal carcinoma

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ABSTRACT

Azygography is a useful technique for the pre-operative detection of unresectability of oesophageal malignancies. Invasion of the azygos vein by oesophageal carcinoma occurs because of the anatomic proximity of the thoracic oesophagus and the azygos vein. Azygography may be performed by either intraosseous injection of a rib or by direct retrograde catheterization. Complete obstruction of the azygos vein indicates that an oesophageal carcinoma is unresectable if no other intrathoracic disease is evident.

Nearly half of carcinomas of the oesophagus, pre-operatively considered surgically curable, at operation are found to be either unresectable or resectable only for palliation (Gunnlaugsson *et al.*, 1970). It is desirable to detect surgically incurable cancers pre-operatively and thus spare these patients an unnecessary operation. As in lung malignancies, azygography may be utilized in staging oesophageal carcinomas (Crummy *et al.*, 1968). This communication relates our experience with azygography in identifying the mediastinal invasion of unresectable oesophageal malignancies.

PERTINENT ANATOMY

The value of azygography in oesophageal carcinoma is based on the close proximity of the azygos venous system and the lower two-thirds of the thoracic oesophagus. The azygos vein is the thoracic continuation of the right ascending lumbar vein. It traverses the diaphragm through the aortic hiatus and ascends on the anterior aspect of the spine to approximately the 4th thoracic vertebral body where it arches forward over the right main bronchus to enter the posterior wall of the superior vena cava. Proximal to its arch, the azygos vein is immediately adjacent to the right posterior aspect of the oesophagus (Fig. 1). Similarly, the hemiazygos vein is the thoracic continuation of the left ascending lumbar vein. It pierces the left crus of the diaphragm, ascends on the left side of the vertebral column, and crosses to the right at approximately the 9th thoracic vertebra to enter the azygos vein. Numerous variations from this classical anatomy are encountered (Gray, 1973; Schobinger, 1964).

TECHNIQUES

There are two commonly utilized angiographic techniques for visualization of the azygos venous system.

Direct catheterization

The azygos vein may be directly catheterized at its entrance into the superior vena cava via the percutaneous femoral vein route. A single-curved or cobra-shaped 6·6 French catheter is used to catheterize the orifice of the azygos vein on the posterior wall of the superior vena cava just above the origin of the right main bronchus. When possible, the catheter is advanced over a guide wire into the descending portion of the vein. Approximately 20 ml. of 76 per cent meglumine-sodium diatrizoate are pressure injected at a rate of 8–10 ml./second. During the injection, a Valsalva manoeuvre may be used to facilitate retrograde filling of the vein. Six films are exposed at one per second in each of the frontal and lateral projections. With this technique the entire azygos vein is usually completely opacified, but the hemiazygos is rarely visualized (Fig. 2).

Intraosseous technique

The most widespread method of azygography is the intraosseous technique by which contrast material is injected into the marrow cavity of a lower rib (Schobinger, 1964). After preparation of the skin with an antiseptic, the soft tissues and periosteum of the 9th or 10th rib in the mid-axillary line, on only the left or on both sides, are infiltrated with local anaesthetic. A small incision is made in the skin and subcutaneous tissues and a 16-gauge bone marrow needle is then inserted with a rotary motion into the marrow cavity of the rib. The needle should initially be held perpendicular to the rib for penetration of the cortex and is then directed posteriorly, parallel to the long axis of the rib, for entrance into the marrow cavity. When in proper position, the needle feels quite rigidly fixed and blood and bone

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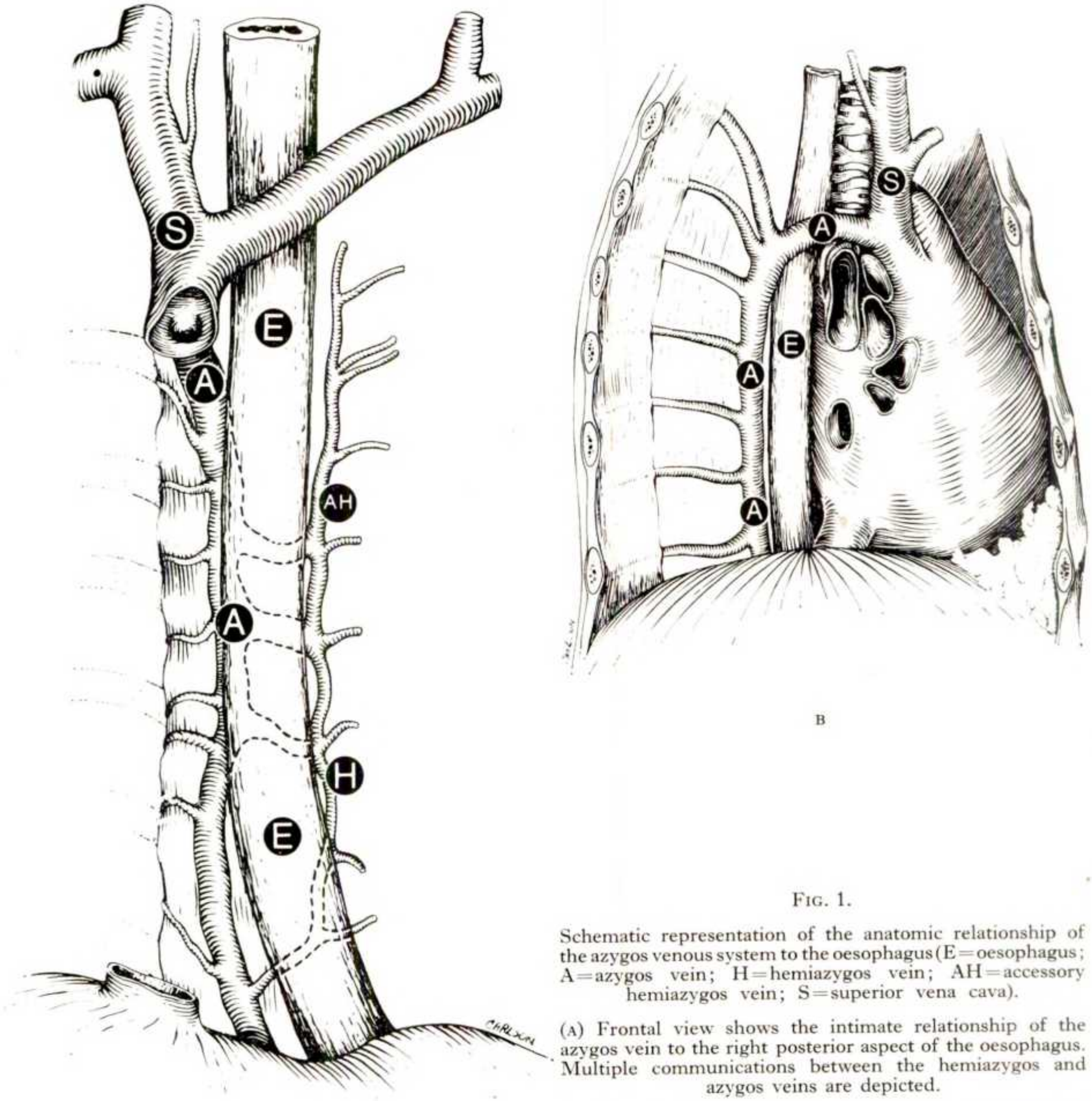

A

B

FIG. 1.

Schematic representation of the anatomic relationship of the azygos venous system to the oesophagus (E = oesophagus; A = azygos vein; H = hemiazygos vein; AH = accessory hemiazygos vein; S = superior vena cava).

(A) Frontal view shows the intimate relationship of the azygos vein to the right posterior aspect of the oesophagus. Multiple communications between the hemiazygos and azygos veins are depicted.

(B) Lateral view shows the parallel course of the thoracic oesophagus and the azygos vein proximal to its arch.

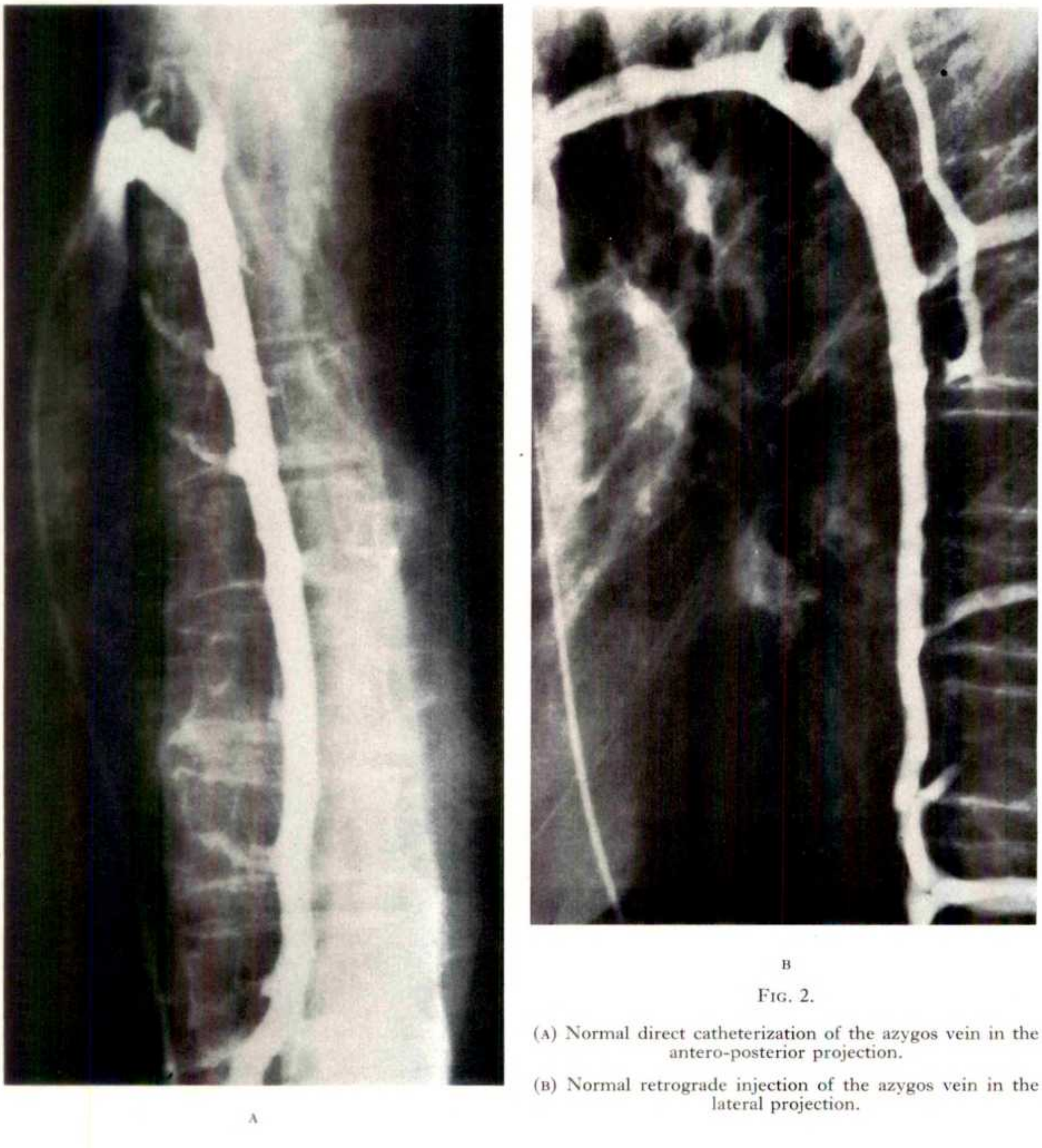

FIG. 2.

(A) Normal direct catheterization of the azygos vein in the antero-posterior projection.

(B) Normal retrograde injection of the azygos vein in the lateral projection.

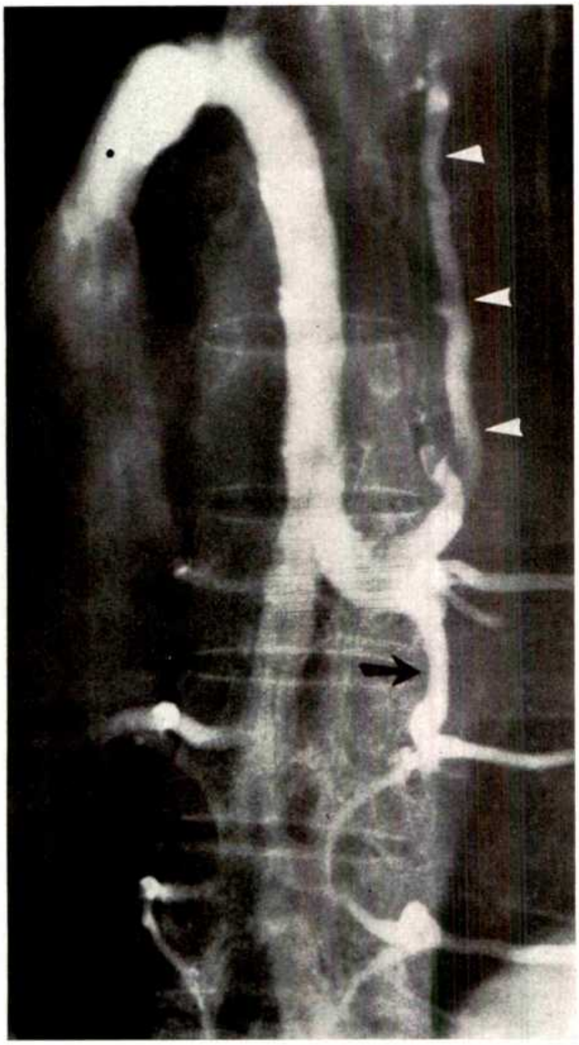

FIG. 3.

Normal frontal azygogram obtained with simultaneous bilateral rib injections. The hemiazygos vein (black arrow) and the accessory hemiazygos vein (white arrow-heads) are also visualized.

marrow can usually be aspirated. A plastic connecting tube is attached to the needle and a small test injection of contrast agent is made. If the needle is correctly placed, the adjacent intercostal vein is immediately visualized. If any significant contrast material extravasates into the soft tissues, puncture of a different rib should be performed. Then 15 ml. of contrast agent are injected by hand at a steady rate over three seconds with six serial films exposed at one per second. A left unilateral rib injection is usually adequate, but the best opacification is obtained with simultaneous bilateral injections (Fig. 3).

INTERPRETATION

Obstruction of the azygos vein has two basic radiographic appearances. One pattern is the demonstration of the actual site of obstruction with or without reconstitution of the vein distal to the obstruction (Figs. 4 and 5). The second pattern is the complete lack of visualization of the azygos vein with collateral flow demonstrated in the vertebral venous plexus (Fig. 6).

DISCUSSION

At the M. D. Anderson Hospital and Tumor Institute patients with carcinoma of the oesophagus undergo azygography if there is no other evidence of unresectability. If the azygos vein is patent, definitive surgery is performed to resect the tumour completely if possible. Unfortunately, some patients with normal azygograms are found to have unresectable lesions at exploration. In our series of 21 azygograms, 12 were normal. Nine patients with normal azygograms underwent operation; four of them had unresectable tumours. This does not reflect inherent inaccuracy in the procedure but rather its limitations since an unresectable oesophageal carcinoma may invade other vital mediastinal structures without involving the azygos vein. On the other hand, obstruction of the azygos vein is strong evidence that a carcinoma of the oesophagus is unresectable. In a series of 33 azygograms done in patients with oesophageal carcinoma reported by Crummy *et al.* (1968), there were eight patients with obstructed azygos veins who underwent operative exploration. All eight were unresectable. In our series of 21 azygograms, nine were obstructed. Only two of these nine patients were explored and both were unresectable. At the present time, if the azygos vein is obstructed, the patient is treated with radiation therapy and/or palliative surgery.

It is important that the radiologic criteria for an abnormal azygogram be stringent to minimize false-positive diagnoses which may deny patients potentially curative surgery. Consequently, extrinsic pressure defects on the azygos vein are not considered evidence of unresectability. For example, we have observed two cases in which defects in the azygos vein in the frontal projection were subsequently shown in the lateral projection to be due to hypertrophic spurs (Fig. 7). Non-neoplastic causes of azygos vein obstruction include lung abscess with reactive lymphadenopathy, sarcoidosis, granulomatous mediastinitis (Wolfel *et al.*, 1966), tuberculous

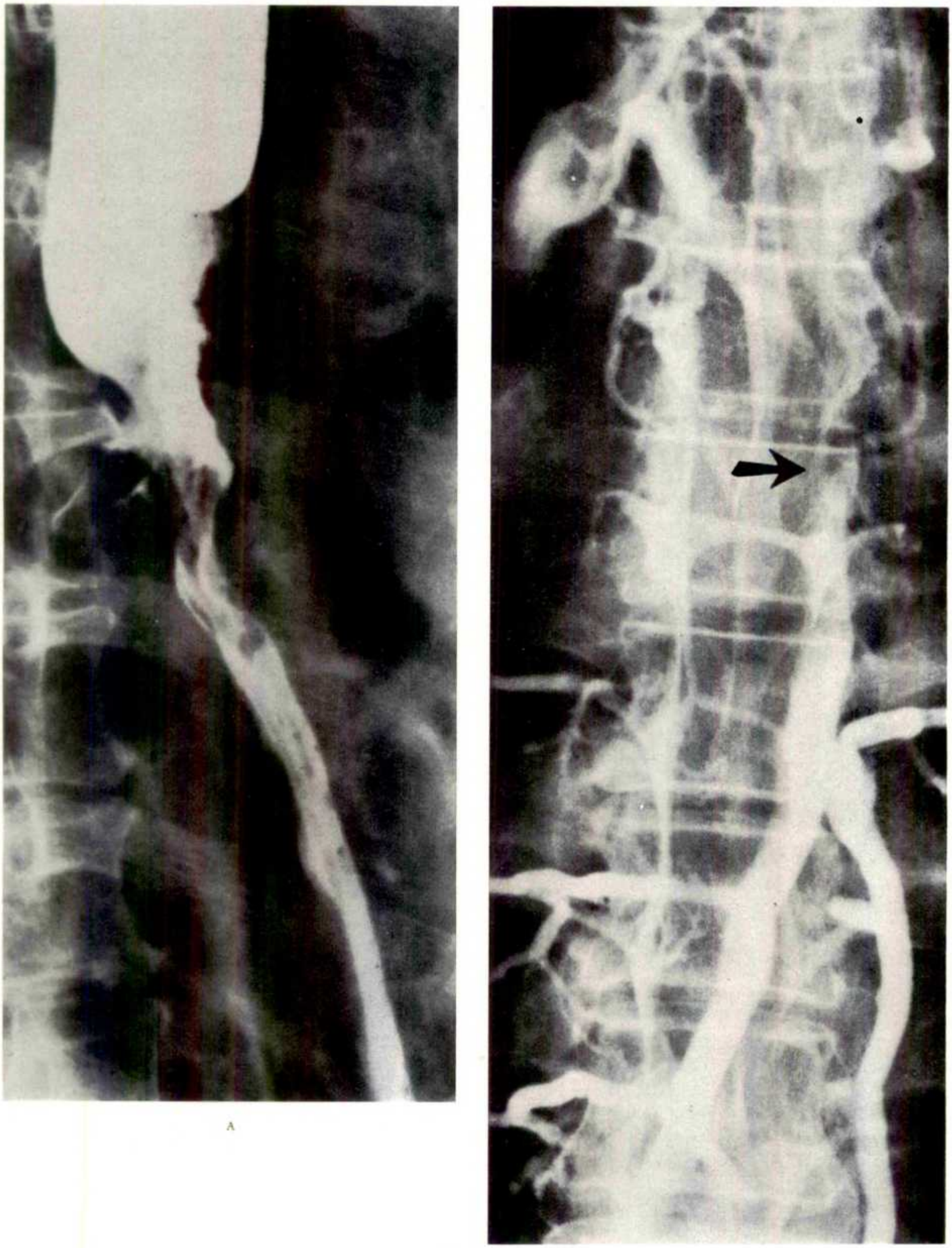

FIG. 4.

FIG. 4 (*opposite page*).

Sixty-year-old male with unresectable carcinoma of the oesophagus.

(A) Oesophagram demonstrates an irregular ulcerating lesion of the mid-thoracic oesophagus.

(B) There is corresponding obstruction of the azygos vein (arrow) at the same level as the tumour with some reconstitution of the azygos arch.

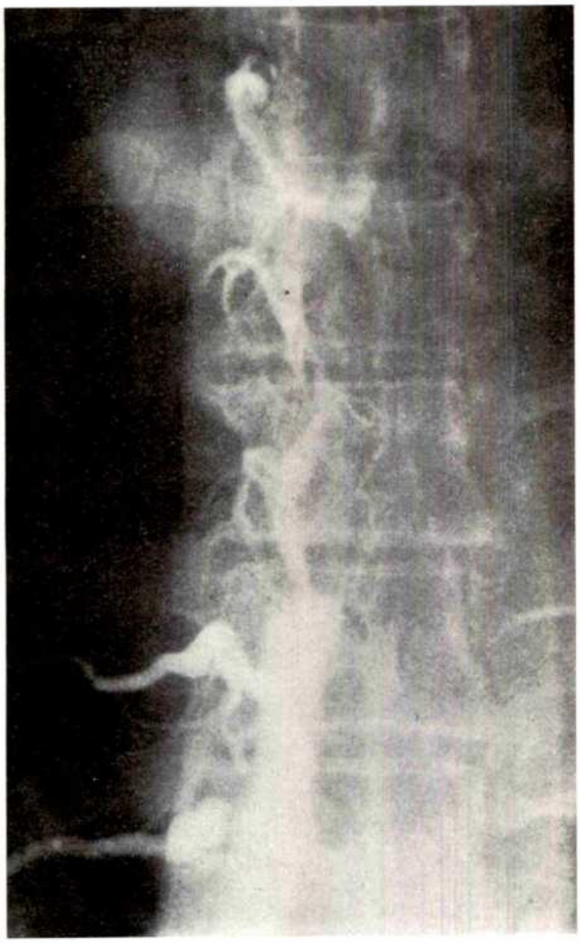

FIG. 5.

Azygography demonstrates total obstruction of the azygos vein from an adjacent oesophageal carcinoma.

pericarditis (Fry *et al.*, 1960), mediastinal fibrosis, (Rinker *et al.*, 1967), and external pressure from a fluid filled left lung cyst (Low *et al.*, 1963). In addition nonvisualization of the hemiazygos vein is not necessarily indicative of involvement by tumour. By retrograde injection, the hemiazygos vein is usually not opacified: by rib technique the contrast agent sometimes flows from intercostal veins to the vertebral plexus and then to the azygos vein, thus bypassing the hemiazygos vein.

At the present time, retrograde catheterization of the azygos vein is our preference since this technique more consistently provides excellent opacification of the azygos vein, is simple to perform, and is less painful than the intraosseous technique. The azygos venous system may also be visualized by injection of one or both ascending lumbar veins with delayed filming of the mediastinum.

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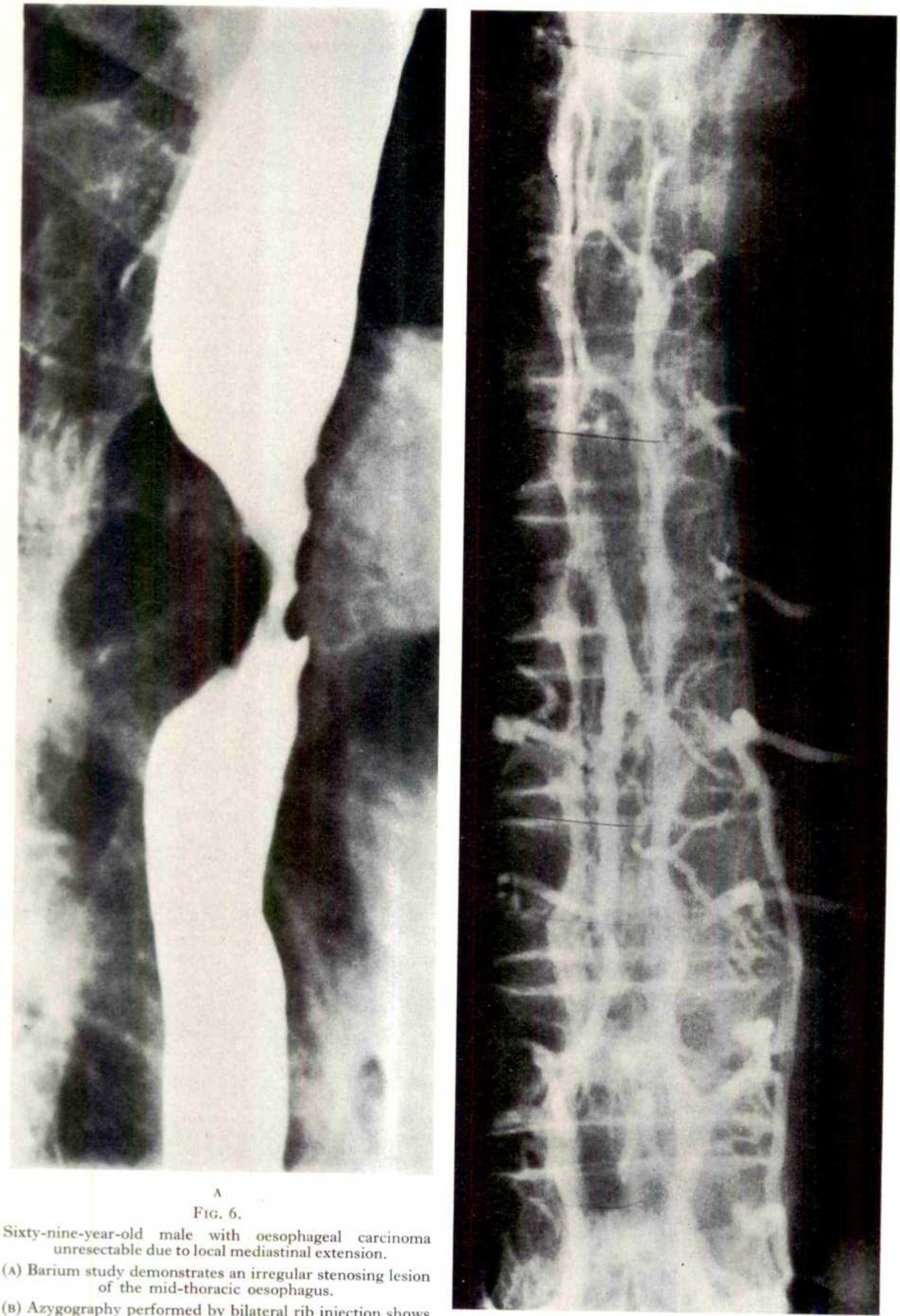

A

FIG. 6.

Sixty-nine-year-old male with oesophageal carcinoma unresectable due to local mediastinal extension.

(A) Barium study demonstrates an irregular stenosing lesion of the mid-thoracic oesophagus.

(B) Azygography performed by bilateral rib injection shows no visualization of the azygos vein with extensive collateral flow in the vertebral venous plexus.

B

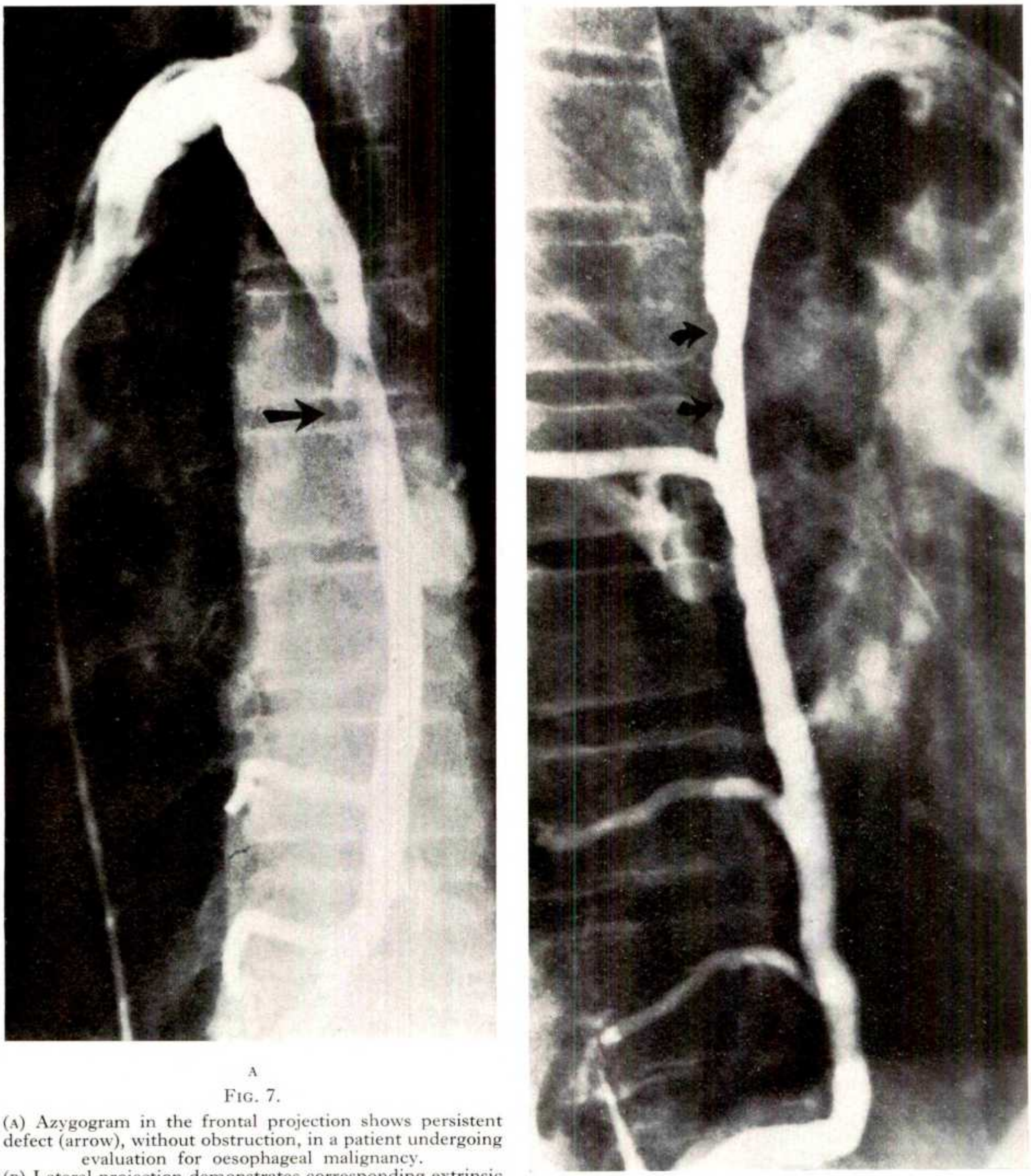

FIG. 7.

(A) Azygogram in the frontal projection shows persistent defect (arrow), without obstruction, in a patient undergoing evaluation for oesophageal malignancy.
(B) Lateral projection demonstrates corresponding extrinsic pressure defects from hypertrophic vertebral spurs (arrows).

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The problem of discrimination in mammography. Arguments for using a biological test object

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Abstract

A specimen of breast tissue containing a carcinoma with multiple calcifications was used as a test object and examined by a range of mammographic techniques. The images were compared with a photograph of the actual specimen which was cleared and stained for calcium salts. A quantitative method of evaluating the discriminating ability of each technique is described and used to compare these images. Xeroradiography and Kodak Crystallex film clearly excelled other imaging methods. The value of using a biological test object is discussed.

A great number of film types and film-screen combinations are now advocated for mammography, each of which has its own characteristics. In trying to establish the potential of one technique in mammography it is thus meaningless to compare its efficiency with any one film system. On the other hand, a trial of all imaging methods used in mammography would be difficult to organize, and it is also doubtful whether any centre would have sufficient numbers of patients to reach a statistically significant result in such a trial.

Comparative studies between different techniques have been few and often their results have conflicted (Ruzicka *et al.*, 1965; O'Mara *et al.*, 1967; Wolfe *et al.*, 1971; Venet *et al.*, 1971).

It thus becomes necessary to compare the different methods by isolating the features that constitute a "good" mammogram and comparing these features, the most important of which is discrimination (Egan 1964; Stanton and Lightfoot, 1964).

Discrimination rapidly improved in the early days of mammography with the introduction of low-sensitivity industrial films which had a high definition (Egan, 1964; Egan and Fenn, 1968). The advent of the molybdenum anode with its softer radiation increased image definition which added further impetus to the use of low-sensitivity film (Gershon-Cohen *et al.*, 1961).

The improvement in image quality was usually at the expense of a higher dose. Some radiologists continued to use the high-definition industrial films claiming that only these showed enough detail (Egan, 1964), other radiologists reacted by introducing faster films needing a lower exposure. The latter progressed to the use of vacuum-packed fast film-screen combinations (Price and Butler, 1974) and more recently to the introduction of a very fast rare-earth element screen (Trimax Alpha 4 system). Although all these steps achieved a reduction in dose, there was usually a concurrent loss of discrimination.

It has been customary to base the choice of mammographic technique on the results of exposure measurements and assessment of discrimination using test objects (Deichgraber *et al.*, 1974; Young, 1974; Deichgraber *et al.*, 1975). The selection of test objects may, however, introduce a bias in favour of one imaging method over another. The purpose of this paper is to indicate means by which this problem may be overcome, and to suggest methods of producing test objects which provide a more realistic prediction of the performance of radiological techniques under clinical conditions. The criteria for detecting disease in the breast are usually of three kinds:

(1) calcification, particularly finer particles,
(2) dense tissue nodules,
(3) spicules of fibrous tissue.

These well established factors have also been selected by computer studies (Ackerman and Gose, 1972). The test object used should be one which allows good discrimination of these three features and in this paper the particular problems relating to calcifications have been considered. The importance of the detection of calcification by mammography in occult breast carcinoma is well established (Venet *et al.*, 1971; Frankl and Rosenfeld, 1975; Millis *et al.*,

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1976). Further work is being done to quantify biological material containing masses and spicules.

Discrimination in any X-ray system is limited in two ways:

(1) by technical factors such as target spot size, spread of the fluorescent light from the screens, etc.;

(2) by statistical fluctuations in the region normally uniform in density as a result of a limited number of grains or photons.

The quality of the image is more severely affected by technical than statistical factors in high-dose systems, but the reverse applies in low-dose systems (Hay, 1964; Rossman, 1966; Van Meeteren, 1973). Any test object used should, if possible, reflect the influence of these deleterious effects on the three typical features found in breast lesions. Regular grids or star patterns do not achieve this, and there is much to be said for using a preparation incorporating biological tissue which includes the foregoing criteria.

When testing the discriminating capacity of xeroradiography against film, another limitation is introduced. Xeroradiography shows an edge better than gradations in density whereas film is more sensitive to small density changes. Therefore the shape and density of the test objects must be the same as those present in breast lesions in order to make a fair comparison. This again favours the use of biological tissues.

In this study subjective rather than objective measurements are used because, providing they can be quantified, they are a truer measurement of the observers performance in detecting lesions. The differences between subjective and objective measurements are modified by the way in which the eye and brain distort the real image making some forms of image easier to see than others. This has been excellently reviewed by Ratcliff (1972).

Subjective images of light and dark bands are formed adjacent to edges between contrasting densities (Mach bands). A possible explanation for these is the inhibition of light receptors immediately adjacent to stimulated receptors in the retina. Experimental work on the eye of the horseshoe-crab supports this hypothesis.

Another effect has been described by Craik and O'Brien (unpublished) where the subjective difference in greyness between two adjacent areas is influenced by density changes at the border between them. A suitable contour at the border can actually make the subjective greyness of adjacent areas the reverse of their objective luminance (the Cornsweet Illusion).

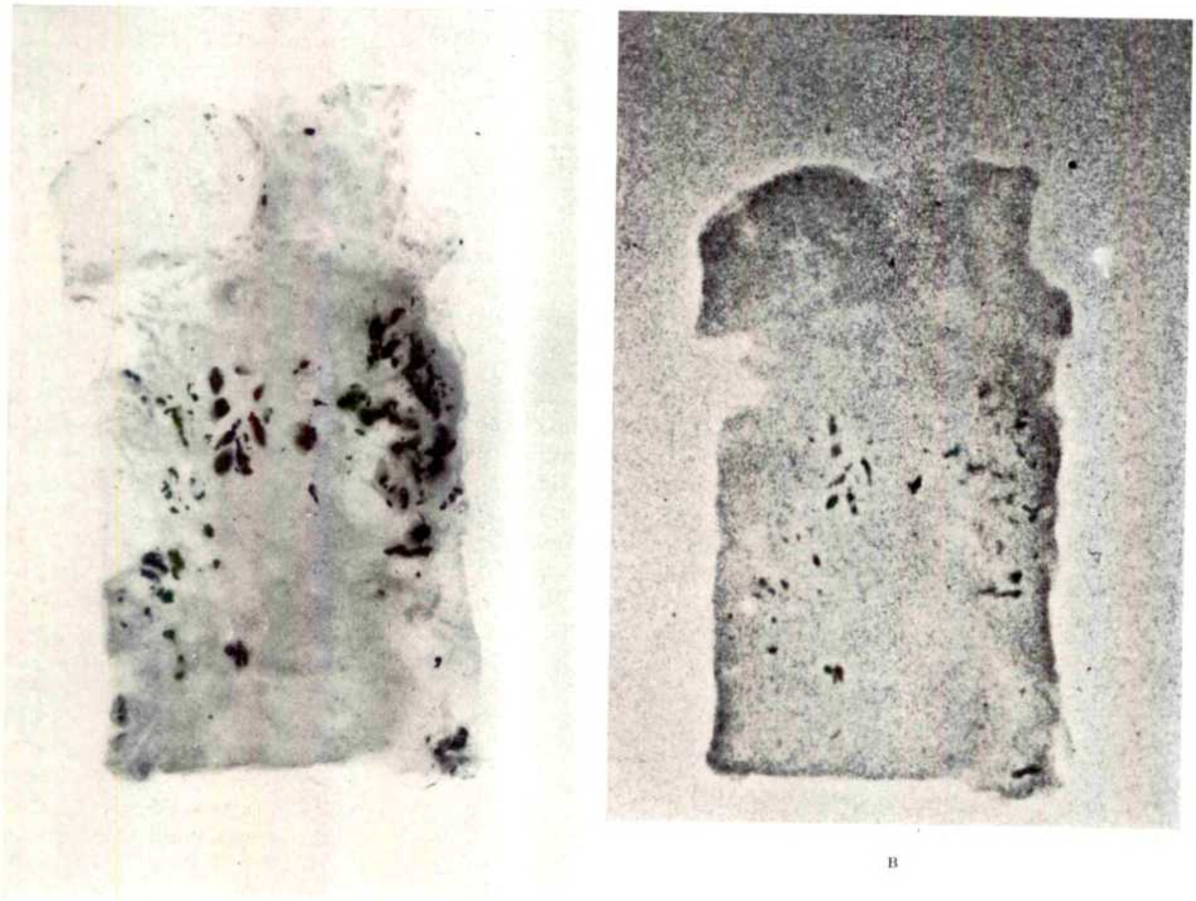
Thus an object seen by an observer is distorted by his optic system and brain into a form which has similar qualities to a xerographic image. It cannot be assumed that further distortion by the eye of a xerographic image favours discrimination when comparing it with a film image, so a subjectively analysed test object must be used.

METHOD

A slice of breast tissue containing an invasive carcinoma was selected for examination. This contained calcifications which measured from 50μ to just over 1 mm in diameter. The specimen was fixed in formalin and divided in half through its sagittal plane. This produced two slices each measuring approximately $2 \times 1 \times 0{\cdot}5$ cm. One was processed and embedded in paraffin to enable a histological section to be cut from the divided surface and stained for calcium salts, this confirmed that the calcifications were within a carcinoma. The other half was cleared using xylol and oil of wintergreen and stained for calcium salts using alazarin red. The tissue was then translucent and the calcifications showed as red opacities. It was photographed across its shortest axis using transmitted light at a magnification of 1:1 (Fig. 1A). Radiographs of the cleared tissue slice sandwiched between a total of 5 cm of fat-equivalent polyester were obtained using two Mammomat units served by the same transformer. One had a molybdenum anode and the other had a tungsten anode. Images were produced at an operating potential of 30 kVp and for xeroradiography at 30 kVp and 50 kVp. The molybdenum anode had a 0·03 mm molybdenum filter and the tungsten a 0·5 mm Al filter, they were otherwise identical and operated at 45 cm FFD. The fat-equivalent polyester was used to simulate an average breast.

The films chosen included a fine-grain industrial film, Kodak Crystallex, a film suitable for automatic processing, Kodak PE4006, and the following film screen combinations: Agfa Gevaert Medichrome vacuum packed with Cronex screen, Dupont Lodose vacuum packed with Cronex screen and 3M Trimax Alpha 4 system. Some examples of the radiographs are shown in Fig. 1B, C, and D. The Kodak PE4006 film was processed using an automatic four minute processor. The Crystallex Film was hand processed (ten minute development). The Medichrome film was developed in a specialized developer. Images of optimum density were produced for all the films by varying the mAs and selecting by densitometry.

The definition of the images was compared.



B

A

FIG. 1

The photographic slide of the cleared specimen was projected to give a ×20 magnification and the outlines of the calcifications were charted onto a fine-quality paper. The image of a Neubaum haematological grid was projected onto the same paper giving calibration squares representing 200+200 μm each. The size of each calcification was then measured using this grid and recorded to the nearest 100 μm mean diameter and classified into one of the following seven size categories: less than 100 μm 100–200 μm, 200–300 μm, 300–400 μm, 400–500 μm, 500–750 μm, 1 mm and over. These categories were numbered 1 to 7, and each calcification was labelled with its relevant group number on the chart.

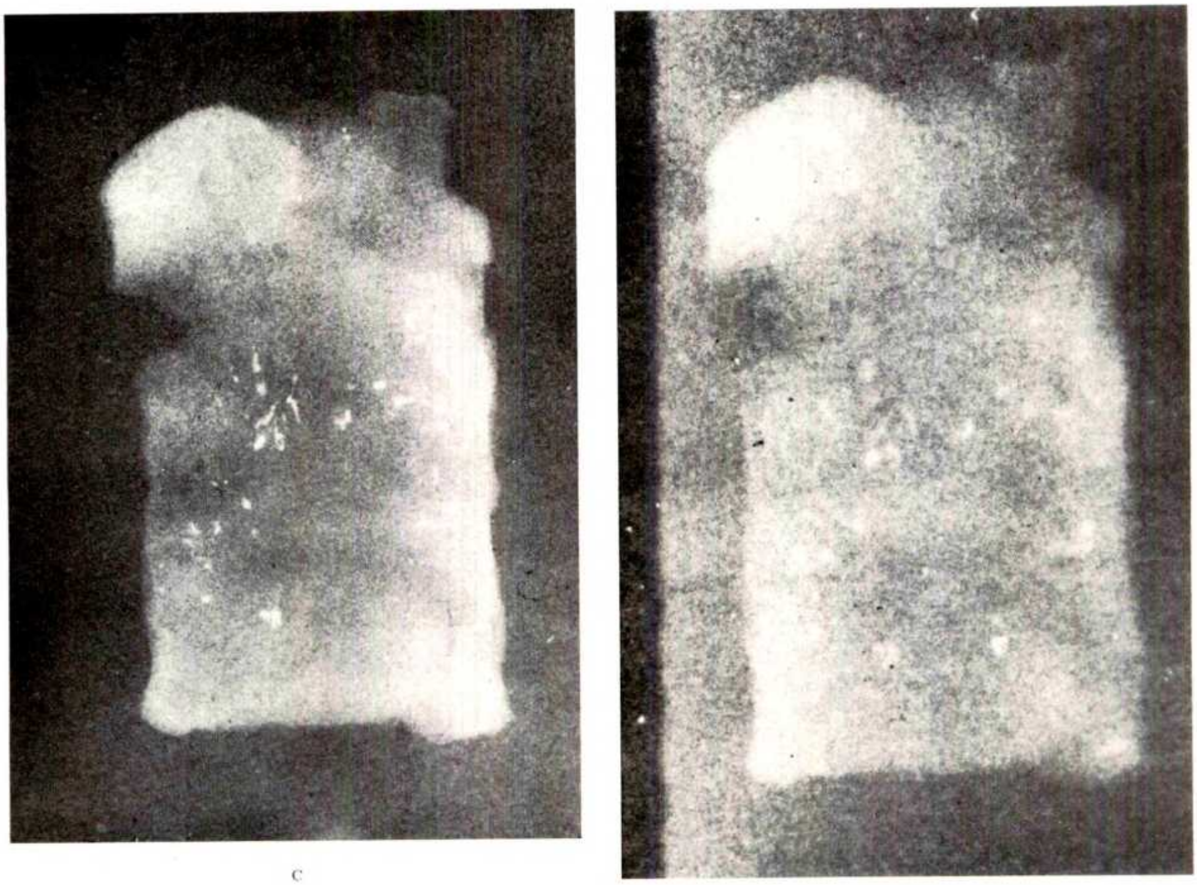
Photographic slides of the xeroradiographs were prepared. These and the actual silver halide film images were projected with the same geometric factors as the cleared specimen onto a screen covered with a clear cellulose sheeting.

Three unbiased observers were asked independently to mark on the cellulose where they thought they saw calcifications. The marked cellulose sheeting was subsequently placed over the chart, and the marks representing the calcifications were counted and the totals for each size group recorded. Marks not corresponding to charted calcifications were noted and recorded as artifacts mistaken for calcifications; other known artifacts unlike calcifications were assumed to have been correctly recognized and ignored by the observers.

RESULTS

The results for the three observers are given in Tables I and II.

They are also recorded as a histogram plotting the number of calcifications observed for each size range selected (Fig. 2). The measurements for all



C

D

FIG. 1.

An illustration of the cleared specimen of breast tissue stained for calcium salts and some of the radiographic images taken of the specimen through 5 cm of fat-equivalent material:
(A) cleared specimen; (B) xeroradiograph W. anode, 0·5 mm Al. at 30 kVp 45 cm FFD; (C) Kodak Crystallex film Mo. anode, 0·03 mm Mo. at 30 kVp 45 cm FFD; (D) 3M Trimax film (Alpha 4 system) Mo. anode, 0·03 mm Mo. at 30 kVp 45 cm FFD.

radiographic imaging methods and for the photograph of the cleared specimen are included.

Most of the calcifications seen in the cleared specimen measured between 100–300 μm. This is in keeping with the findings of Millis *et al.*, 1976, who, in a study of calcification in malignant and benign breast disease, found that most carcinomas contained calcification in this size range. The range of calcifications can therefore be regarded as representative of those found in breast carcinomas, a premise used in interpreting the results which follow.

When comparing the measurements for the radiographs with those of the cleared specimen several observations can be made:

(1) Calcifications larger than 500 μm average diameter were shown by all the methods except Medichrome and Trimax Alpha 4 system.

(2) Only a small proportion of the calcifications under 400 μm in diameter were detected by all methods. For example, no more than half the calcifications between 200–300 μm were shown by any method. Some carcinomas contain only calcification of this size (Millis *et al.*, 1976).

(3) Many calicfications smaller than 100 μm in diameter were present, but these were not demonstrated by any of the methods.

(4) In the important range of calcification size between 100 and 300 μm four methods were clearly superior, *viz.*

TABLE I

Number of calcifications counted on each film image by three independent observers compared with the total count seen in the cleared specimen

Largest mean diameter of calcification in μm	Number of calcifications seen (three observers) for each film imaging method					Cleared specimen
	Kodak Crystallex	Kodak PE4006	Dupont Lodose (Cronex screen)	Agfa Gevaert Medichrome (Cronex screen)	3M Trimax (Alpha 4 system)	
100	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	23
200	5, 5, 5	4, 5, 4	3, 3, 3	3, 2, 1	1, 1, 1	47
300	18, 17, 19	7, 4, 8	6, 6, 6	6, 3, 6	4, 3, 5	40
400	11, 11, 11	10, 8, 11	7, 7, 7	6, 4, 5	6, 6, 6	16
500	7, 7, 7	7, 5, 7	8, 7, 7	5, 5, 5	6, 6, 6	9
750	9, 8, 8	8, 8, 8	8, 8, 8	7, 7, 7	7, 6, 8	8
1000	8, 8, 8	8, 8, 8	8, 8, 8	8, 8, 8	5, 3, 6	8

TABLE II

Number of calcifications counted on each xeroradiographic image by three independent observers compared with the total count seen in the cleared specimen

Largest mean diameter of calcification in μm	Number of calcifications (three observers) for each xeroradiographic combination of target element and generating kVp				Cleared specimen
	Mo 30	Mo 50	W 30	W 50	
100	0, 0, 0	0, 0, 0	0, 0, 0	0, 0, 0	23
200	8, 7, 8	6, 6, 6	6, 6, 6	3, 3, 3	47
300	15, 14, 16	16, 14, 14	14, 14, 14	8, 7, 6	40
400	11, 10, 12	10, 8, 8	8, 8, 10	8, 8, 8	16
500	7, 7, 7	6, 6, 8	7, 7, 7	7, 7, 7	9
750	8, 8, 8	8, 8, 8	8, 8, 8	8, 8, 8	8
1000	8, 8, 8	8, 8, 8	8, 8, 8	8, 8, 8	8

(a) Kodak Crystallex (hand developed),
(b) xeroradiography.
    (i) with Mo target at 30 kVp;
    (ii) with W target at 30 kVp;
    (iii) with Mo target at 50 kVp.

(5) Of the remaining silver halide film methods the other non-screen film, Kodak PE4006 showed a relative improvement for the larger calcifications (> 400 μm).

(6) All the film-screen methods were uniformly poor over the full range of calcification sizes.

(7) There was very little difference in discrimination of calcifications between the best four methods. Xeroradiography tended to show more calcifications of less than 200 μm in diameter but Kodak Crystallex was better in the 200–300 μm range.

(8) The number of artifacts misinterpreted as calcifications did not differ greatly between film without screen, film with screen and xeroradiography.

(9) The performance of xeroradiography was independent of the target used (molybdenum or tungsten) provided that a low kVp was employed.

(10) When using a high kVp the calcifications were well shown by xeroradiography with the molybdenum target. Using a tungsten target at

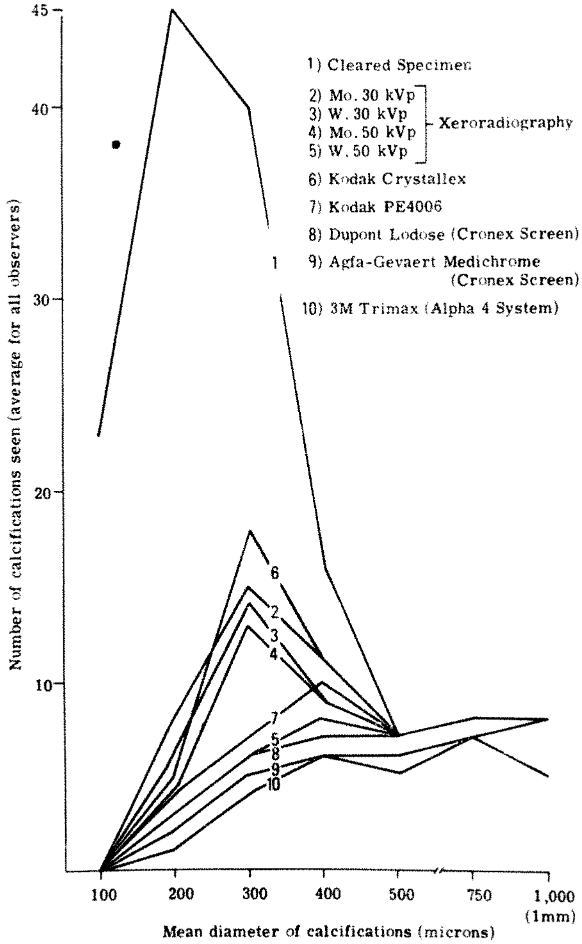


FIG. 2.

Average calcification counts of three observers are plotted against particle size for each radiographic image. The count in the cleared specimen is included for comparison.

50 kVp the calcifications were shown less well than at 30 kVp but it was still better than any film screen combination tested.

DISCUSSION

Although there is often much debate about the diagnostic significance of calcifications in the breast, it is generally accepted that the most frequent indicator of a clinically occult carcinoma is the detection of calcifications by mammography (Venet *et al.*, 1971; Rogers and Powell, 1972). Unfortunately, no form of mammography can be claimed to detect all the calcifications that can be demonstrated by histology (see Table III), or by radiography of tissue slices (Fisher *et al.*, 1975).

TABLE III

INCIDENCE OF CALCIFICATION DETECTED IN CARCINOMA OF THE BREAST BY MAMMOGRAPHY AND BY HISTOLOGY GIVEN AS PERCENTAGES OF TOTAL CARCINOMAS SEEN

Recording medium	*By mammography*	
Silver halide film	Levitan *et al.*, 1964	29%
	Black and Young, 1965	30%
	Friedman *et al.*, 1966	24%
	Gravelle, 1975	40%
	Nunnerley, 1975	54%
Medichrome film	Price, 1975	36%
Xeroradiography	Wolfe, 1974	51%
	Gravelle, 1975	61%
	Millis *et al.*, 1975	48%
	By histology	
	Levitan *et al.*, 1964	58%
	Koehl *et al.*, 1970	62%
	Fisher *et al.*, 1975	60%
	Millis *et al.*, 1975	63%

Two approaches have been used to compare the discriminating capabilities of the various mammographic techniques. One is to compare the percentage of calcifications seen in carcinomas by the various mammographic techniques used at different centres. The results of some of these surveys are shown in Table III. The other way is to apply the various mammographic techniques to a phantom containing calcifications.

When comparing series from different centres no account can be taken of the influence of the variations in technique other than the actual recording device used. In the second approach it is difficult to be sure that the phantom reflects all the features of real tumour calcifications.

The present study has been aimed at eliminating some of these difficulties. The findings substantiate the reports that only a small percentage of calcifications are seen by any form of mammography (Table III) but emphasize that the size of the calcifications is not the only feature that determines their radiographic visualization. It was also found that different techniques show differing proportions of calcifications for each size range. It is probable that breast calcifications contain a variable concentration of calcium salts and that those with little calcification in them tend to be more indeterminate in outline. This may explain why xeroradiography appears less efficient than high contrast film (Crystallex) in the 200–300 μm range. The larger calcifications containing low concentrations may not have given such a striking edge effect and would only be seen by their gradual change in density, a feature better shown by film. On the other hand the very clear superiority of xeroradiography in the 100–200 μm range could be explained by the edge effect facilitating discrimination of very small opacities whatever their density, whereas for film a larger density difference is required for discrimination as the particles get smaller.

The results also show that the loss of discrimination due to the use of screens produces a measurable reduction in the number of calcifications seen in the important size ranges 100–300 μm. It is interesting to note that in Table III the best results for a mammographic technique using film were achieved with a fine-grain industrial film without screen (Nunnerley, 1975).

In this study Kodak PE4006 (without a screen) can be seen to make a relative recovery in its detection rate for the larger calcifications when compared with Kodak Crystallex. This may be because a greater area of differing density is needed to show a lesion due to its low contrast. The comparisons of images produced by molybdenum and tungsten anodes were only made for xeroradiography as only with this method is there serious argument about the preferable anode and tube potential to be used. Figure 2 shows that of the xeroradiographic régimes examined, only the tungsten anode at 50 kVp was poor. This is explained by the differences in image quality determined by the radiation spectra even for xeroradiography. Most of the spectrum produced by the molybdenum anode consists of characteristic radiation of low keV irrespective of the generating potential (Boag, 1973; Marshal *et al.*, 1975). It can be seen from Fig. 2 that there is a wide range of discrimination for the various methods tested and that there are large differences in the detection of calcifications in the clinically important range.

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Book reviews

Clinical Scintillation Imaging. By Leonard M. Freeman and Phillip M. Johnson, pp. 820, 2nd end., 1975 (New York, Grune & Stratton), £26·80.

In the first edition of this book, published in 1969, the authors recognized that it was no longer possible for one individual to have equal expertise in all aspects of scanning, and invited many recognized authorities to contribute. What was true then is even more true now, and 31 hand-picked contributors have combined to write this authoritative book. The key to its success is that the contributors are on their mettle to live up to their international reputations, and each chapter is based on a wealth of knowledge, beautifully illustrated on high quality paper.

The method of presentation is straight-forward and relatively unimportant. There are six chapters in the first section, devoted to fundamental consideration; these include a historical chapter by the late Benedict Carsen, in which the debt of the discipline of nuclear medicine to the scientific pioneers is clearly recorded. This section includes comprehensive accounts of radioactive agents, instrumentation, image formation, dynamic function and radiation safety. The chapter on radiation safety draws attention to the current interest in reducing radiation dosage to patients and underlines the idea of "benefit versus risk", in which a greater radiation dose is acceptable if the likelihood of detecting a lesion is high, and goes on to say that the absorbed radiation dose is often less than from the corresponding X-ray procedures. This leaves some unease about possible misinterpretation of "corresponding". Part of the case for scintillation imaging is that in most instances there is no truly "corresponding" X-ray procedure, and the activity used should be the minimum needed to give a satisfactory study. A more telling argument is made in the preface where the annual whole-body absorbed dose in the USA in 1970 for diagnostic X rays (72 mrem) is compared with that for radiopharmaceuticals (1 mrem).

The second part of the book is concerned with clinical considerations, and each major system is discussed in great depth. Each chapter has a substantial reference list. Then there is a chapter on recent advances in which the authors have succeeded in including pyrophosphate myocardial imaging and urokinase venography. The final chapter is concerned with the future, in which the advances of the next decade are predicted as more gradual than those of the last decade, allowing time for consolidation. There is an excellent glossary and a comprehensive appendix of radionuclides.

The reasoning and reasonableness of all the contributors is admirable, and it is self-evident to anyone who has read this book that no-one will fail to benefit from studying it. It is a large book that should be on the bench of every scanning department.

It is no fault of the authors that the terminology of this discipline is unsatisfactory and the very title is something of a mouthful despite the subtle renaming of the second edition. No speakable alternative springs to the mind or the tongue and it would be impudent to try to coin yet another word.

It has always been necessary to read more than one book in order to grasp the essentials of any speciality and nowadays there is more scope than ever for doing so. This volume deserves a high place on anyone's reference list.

E. Rhys Davies.

Medical Terminology in Hospital Practice. 2nd Edition. By Paul M. Davies, pp. 381, 1974 (London, William Heinemann Medical Books Ltd), £2·75.

This is a useful reference book for the student, particularly students of radiography. It is neither a dictionary nor a textbook, but gives descriptions and explanations of terms related to medicine, general pathology and diseases of various body systems. In addition, the book elaborates on the radiological aspects of the topic in question, and is the sort of book one would wish to have immediately to hand in a department, to encourage the student to develop an inquiring mind. Indeed we have found the first edition of this book a valuable asset to all members of staff, and I am sure that the second edition will prove equally popular.

Susan Styles.

1976, *British Journal of Radiology*, 49, 686–689

Irradiation to the thyroid gland at cardiac catheterization and angiocardiography in children

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ABSTRACT

Irradiation to the thyroid gland was measured during cardiac catheterization in 16 infants and 30 children aged 1 to 13 years. The doses from fluoroscopy, full-scale angiocardiography, and cineradiography were measured separately with thermoluminescent dosimeters and, in addition, the exposure-area product was assessed during fluoroscopy with a transparent ionization chamber.

Median value of the absorbed dose to the thyroid from the complete heart investigation was 370 mrad in infants and 260 mrad in children. The highest values and also the greatest range in dosage were observed in infants. The quotient of the thyroid-absorbed dose divided by the integral dose or the dose per exposed film area was also highest in infants, due to anatomical conditions. The absorbed dose to the thyroid during heart catheterization comes almost exclusively from scattered radiation. By appropriate examination technique this dose can be kept within acceptable limits.

The use of cardiac catheterization and angiocardiography in investigating heart disease may involve high radiation dose to the patient. Several reports have appeared in the literature concerning this risk (Ardran *et al.*, 1970; Carlsson, 1965; Gough *et al.*, 1968; Kaude and Svahn, 1974; Rowley, 1974). The radiation exposure to infants and children is of particular significance, *inter alia* since radiosensitive organs lying outside the primary examination field may also receive high doses of radiation.

Radiation exposure to the thyroid gland at heart catheterization and angiocardiography in children has recently been studied by Maripuu (1974). He found that the absorbed dose to the thyroid gland varied between 0·57 and 9·12 rad in patients aged 0–13 years. When studying integral and gonad doses during angiocardiographic procedures, Kaude and Svahn (1974) found by chance in a six-year-old child that the absorbed dose to the thyroid gland was 800 mrad (Svahn, personal communication). Considering the radiosensitivity of the thyroid gland (BEIR Report 1972; Dolphin, 1968; Dolphin, 1972; UNSCEAR Report, 1972) and the increasing use of angiocardiography in infants and children, these observations give rise to a demand for further investigation of unintentional irradiation of the thyroid gland in connection with angiocardiographic procedures.

MATERIAL AND METHODS

The investigation was carried out during the periods November 1972–May 1973 and November 1973–February 1974 and comprised 46 patients; 16 patients aged one year or less (infants) and 30 patients aged 1·1–13 years. Angiocardiography always included frontal and lateral projections. During full-scale radiography, 14 sets of paired exposures were made for left-heart catheterization, and 18 sets of paired exposures for right-heart examination. The length of the cine recordings was determined by television monitoring. The patients may be subjected to catheterization of both the left and the right side of the heart and to several angiocardiographic studies at a single examination. In the presentation of the results no specification is made as to which side of the heart was subjected to investigation, or if both sides were examined.

Diagnostic equipment and technique

Televised fluoroscopy was performed with a 25/15 cm image intensifier with automatic brightness stabilization. Exposure rate on the input screen of the image intensifier was 15 μR/s in about two-thirds of the cases and 30 μR/s in the remaining cases. Fluoroscopy and filming with a vertical beam was performed with an undercouch tube. For full-scale radiography an overhead tube was used. Fluoroscopy in the lateral plane was rarely used.

Filming was done with pulsed 35-mm cineradiography at a frame rate of 75 frames s^{-1} with automatic exposure control (exposure 12 μR/frame on the input screen of the intensifier). Full-scale serial radiography was performed with an Elema Schönander cut-film changer. The exposure to the film was approximately 1·2 mR (automatic exposure control was not used). The tube voltage varied between 50 kV and 80 kV in fluoroscopy and between 60 kV and 95 kV in filming and serial angio-cardiography. Siemens special intensifying screens were used.

Method of absorbed dose measurement

The dose to the thyroid region was measured with extruded LiF ($3\times3\times1$ mm) thermoluminescent dosimeters, read out on a Harshaw 2000 instrument. Calibration of each dosimeter separately was

TABLE I

THE THYROID ABSORBED DOSE AT HEART CATHETERIZATION AND ANGIOCARDIOGRAPHY PERFORMED IN 16 INFANTS AND 30 CHILDREN. THE DOSE CONTRIBUTION FROM EACH PROCEDURE WAS MEASURED SEPARATELY. THE DOSES ARE EXPRESSED IN mRAD, THEIR DISTRIBUTION IS EXPRESSED IN TERMS OF MEDIAN VALUE, TOTAL RANGE AND SEMI-INTERQUARTILE RANGE BETWEEN THE FIRST AND THIRD QUARTILES $(Q_3-Q_1)/2$.

	Age ≤ 1				1 < Age ≤ 13			
Procedure	Number of procedures	Range mrad	Median mrad	$\frac{Q_3-Q_1}{2}$ mrad	Number of procedures	Range mrad	Median mrad	$\frac{Q_3-Q_1}{2}$ mrad
Fluoroscopy	16	18–970	105	54	28	4–358	39	25
Serial angiocardiography	11	74–491	172	57	27	32–337	119	46
Cineangiocardiography	6	95–320	130	76	17	50–183	109	32
Total thyroid absorbed dose at heart catheterization and angiocardiography	16 patients	117–1,630	369	149	30 patients	86–548	261	82

performed in air, the dosimeter being placed in a paper bag close to an ionization chamber and exposed at 60 kV tube voltage with a total filtration of 4 mm Al (approximate half-value layer 2·8 mm Al). The quality of this radiation is representative of the quality of the primary and scattered radiation emitted during the diagnostic X-ray procedures. Within this energy range the sensitivity of extruded LiF dosimeters is fairly independent of the variation in quality of the radiation which may occur during röntgen examination (Endres *et al.*, 1970). To calculate the absorbed dose in the soft tissue a factor of 0·92 rad R^{-1} was used. A total of 30 dosimeters was used in the investigation: six of these constituted control dosimeters, checked in a fixed geometry with a ^{137}Cs-source. Before each measurement the dosimeters were annealed for 1 hour at 400°C (pre-irradiation annealing). For the six control dosimeters, irradiated on eight different occasions, the coefficient of variation of the relative calibration factors varied between 1·8 per cent and 3·0 per cent. Inaccuracy due to variation in dosimeter response with varying tube voltage is considered to be ±2 per cent at most. Total error in the measured absorbed dose is within 10 per cent. Using the peak reading of the glow curve, the lowest dose that could be measured was about 4 mrad.

During measurement the dosimeters were enclosed in pairs in cellophane bags, and one such bag was applied to each side of the neck, adjacent to the left and right lobe of the thyroid, respectively. The mean value of four dosimeters was taken to represent the absorbed dose to the thyroid in each patient.

To measure the total dose delivered to the patient during fluoroscopy, the mean energy imparted (the integral absorbed dose) was calculated from measurements of the exposure-area product by a transparent plane-parallel ionization chamber placed on the undercouch tube (Carlsson, 1963). Except in a few cases, the contributions to the total thyroid dose from fluoroscopy, full-scale angiocardiography, and cineradiography, were measured separately.

RESULTS

Fluoroscopy

The absorbed dose to the thyroid is given in Table I. The highest values and also the largest dose variation were observed in the infants. The median value of the fluoroscopy time was 14 minutes for infants (measured in 14 cases) and 12 minutes for children (18 cases).

The integral absorbed dose from fluoroscopy and the exposure-area product was measured in 27 patients and the results are given in Table II.

The ratio between the thyroid absorbed dose and the integral absorbed dose was largest in the infants (Fig. 1).

Serial angiocardiography

The absorbed doses to the thyroid are given in Table I. The median value of the contribution to

TABLE II

Earlier and present results of measurements of integral absorbed dose and exposure-area product at fluoroscopy in connection with heart catheterization in infants and children

	n	Integral dose kg rad Mean	Integral dose kg rad Median	Exposure-area product R cm^2
Kaude and Svahn (1974)	14	3	—	—
Rowley (1974)	82	—	—	145–177
Blomgren and Bergman (1973)	4	3·8	3·3	—
Present authors				
Infants	10	1·9	1·3	250 (median)
Children	17	3·3	2·8	420 (median)
Total	27	2·8	1·8	

n = number of procedures

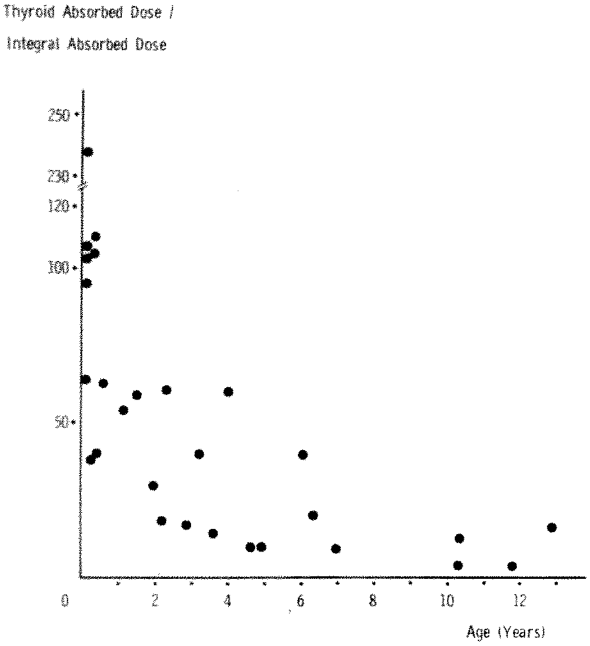

Fig. 1.

The ratio between the thyroid absorbed dose (mrad) and integral absorbed dose (kg rad) at fluoroscopy related to the patient's age. The figure shows that, for the same integral dose at fluoroscopy, the thyroid is more exposed in infants and young children than in older children.

the thyroid absorbed dose was 8·0 mrad from the exposure of each film-pair (one film in lateral and one in frontal projection) in infants and 6·4 mrad in children.

Cineradiography

The mean time for cine recordings was 7·9 seconds (total 1,185 frames). Absorbed doses to the thyroid are given in Table I. The median value of the contribution to the thyroid absorbed dose from the exposure of each pair of frames was 0·33 mrad in infants and 0·19 mrad in children. The thyroid absorbed dose per exposed film area was substantially higher in infants than in children (Fig. 2). The difference between infants and children in this respect was not present when bi-plane serial radiography was performed.

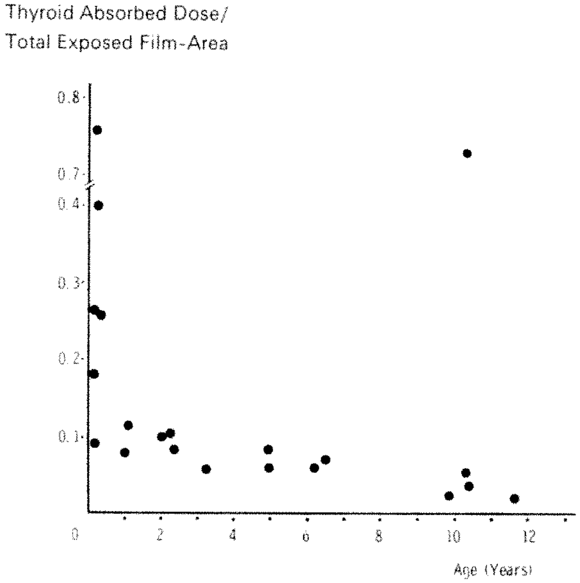

Fig. 2.

The ratio between the thyroid absorbed dose (mrad) and the product of the number of cine frames multiplied by the exposed area per frame (= total exposed film area in cm^2) related to the patient's age. The dose contribution to the thyroid per exposed film area is larger in infants and young children than in older children.

Discussion

The absorbed dose to the thyroid comes almost exclusively from scattered radiation. Therefore, measurements made on the neck are fairly representative of the absorbed dose to the thyroid. Phantom measurements confirmed this.

The magnitudes of the quotients of the thyroid absorbed dose divided by the integral absorbed dose, and by the dose per exposed film area, indicate how far from the thyroid gland the radiation field is situated. These quotients were greater in infants than in children. This is easily understood from the anatomical conditions. However, the difference between infants and children was less marked at biplane serial radiography. This must be due to the fact that the radiation field is less carefully collimated in serial radiography than in cineradiography.

The integral absorbed dose in the present study was in agreement with earlier reports (Blomgren and Bergman, 1974; Kaude and Svahn, 1974). However, the exposure-area product was twice as large as that reported by Rowley (1974); a different age distribution of the patients may possibly explain the difference.

In children aged five years or more, the contribution to the thyroid absorbed dose from fluoroscopy in this study was equal to that found by Maripuu (1974). However, the latter author found the median value of the total thyroid absorbed dose from both fluoroscopy and full-size angiocardiography to be 2·5 rad in infants (four cases) and 3·9 rad in children (nine cases). These high values are due partly to excessive field sizes, partly to the larger number of exposures used as compared with the present study.

Conclusion

The median value of the total absorbed dose to the thyroid from the heart catheterization procedure was, in the present study, 370 mrad in infants and 260 mrad in children. The doses are considerably lower than those reported to have induced thyroid malignancies. The dose may be increased tenfold if an inappropriate technique is used.

According to estimates of the effect of irradiation (the BEIR Report, 1972; Dolphin, 1968; Dolphin, 1972; UNSCEAR Report, 1972), the risk of thyroid cancer after heart catheterization of infants and children including angiocardiography performed with appropriate techniques need not be increased by more than $1\text{–}4 \times 10^{-5}$.

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Book review

Traité de Radiodiagnostic, Vol. 14. Part 1, pp. xviii+732, 1975. (France: Masson et Cie), 790 ff.

The volume is part of the encyclopaedia *Traité de Radiodiagnostic* written in French, which gives an excellent account of modern radiology.

It deals with the abnormal skull and brain in considerable detail, but only a general description of the effects of cerebral tumours is included because they will be considered in Part 2.

It is a balanced, well set out text book, sufficiently comprehensive for routine reference and supplemented by a good selection of references from both the continental and English literature. The value of C.A.T. is clearly emphasised, but, perhaps because it is only now becoming universally available as a routine test, it is not given the space it merits in some chapters.

The work is beautifully produced and profusely illustrated with well selected radiographs, all of which are of excellent quality, so that it could be used as an atlas. It reflects the high standard of French neuroradiological practice and is strongly recommended as a first class account of modern neuroradiology.

B. E. Kendall.

1976, *British Journal of Radiology*, *49*, 690–699

Tolerance of rodent tails to necrosis after "daily" fractionated X rays or D-T neutrons

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ABSTRACT

The rat tail has been used as a model system to study the necrosis of an organized tissue following fractionated doses of collimated D-T neutrons or 290 kV X rays. RBE values for tail tolerance – 10 per cent of tails necrosing after the early skin reactions – rise from about 1·7 (single doses) to about 3·1 (16 fractions in 22 days). Neutron tolerance doses are almost independent of fractionation from 2 to 16 fractions.

The tissues at risk are shown to be rather hypoxic. Early skin reaction levels can be used to predict the fraction of tails that will necrose. Early peak reactions for a given fraction of necrotic tails were slightly higher for neutrons than for X rays, and this difference was consistent for all the dose fractionation schedules employed.

The success of tumour radiotherapy is limited by the "tolerance" of surrounding irradiated normal tissues. A failure of the normal tissue to heal in 10 per cent of cases is usually regarded as an upper limit to acceptable (tolerance) levels in clinical practice. The renewed interest in high linear energy transfer radiotherapy, for reasons of tumour oxygenation (Fowler *et al.*, 1963a) has led to a reassessment of tolerance dose levels for such radiations. These levels are now reasonably well established for cyclotron-produced neutrons (16 MeV D on Be), and one standard treatment régime is 1,560 rad in 12 fractions over 26 days (Catterall *et al.*, 1971 (1975 dosimetry)). These values were based on experimental work using skin reactions in rodents and pigs (reviewed by Field, 1969) and man (Morgan, 1967).

The development of a compact D-T (deuterium on tritium) generator of 14–15 MeV neutrons for radiotherapy, with beam quality and collimation different from that of cyclotron beams, requires the establishment of tolerance doses for this quality of radiation. The expected lesser biological effectiveness of D-T neutrons than cyclotron-produced neutrons using 16 MeV D on Be is shown, for example, by a comparison (Hendry and Greene, 1975) of published RBE values for mouse intestinal damage. New types of radiation in therapy are usually tested initially on skin reactions. Unfortunately, established experimental systems with small animals for measuring skin damage, *e.g.* on rodent feet (Fowler *et al.*, 1965), are difficult to use with D-T neutron beams, because of the greater inherent problems in collimating the higher energy neutron beams to prevent lethality in small animals. Also, the need is emphasized by radiotherapists for model *in vivo* systems where damage to regions of the body comprising several tissue types is involved, as this parallels the clinical situation. We have therefore developed a new system, based on the response of the longest extremity in the rodent—the tail. The system is described in terms of initial skin reactions and tail healing/necrosis rates, and iso-effect data are presented for various fractionation schedules up to 16 fractions in 22 days.

MATERIALS AND METHODS

Animals

Ten- to 12-week-old female (C57BL♀ × DBA2♂)F_1 hybrid mice were used for the basic studies on tail response, and three-and-a-half to four month old female albino Wistar rats for the fractionation work. Four to six mice were used per dose group, six to nine rats per group for X rays, and eight rats per group for neutrons. As each experiment was usually repeated, these numbers were doubled in most cases.

X-irradiations

Orthovoltage X rays were produced by a Siemens Stabilipan unit operating at 290 kV, 12 mA and with HVL of 2 mm Cu. The dose-rate was 430 rad minute^{-1} for mouse tails, and 250 rad minute^{-1} for rat tails. Individual unanaesthetized mice were constrained in perforated adjustable Perspex tubes, and 12 were positioned radially on a horizontal board with the tails pointing to the centre and situated in radial holes in a Perspex disc (1 cm thick, 9 cm radius). Lead shielding 3 mm thick allowed only the mid 2 cm of each tail to be irradiated, with minimal whole-body dose ($<$ 2 per cent). A heating coil and thermostat underneath the disc enabled the temperature in the tail holes to be maintained at about 37°C if required, and a gas inlet was provided to all tail holes in the disc. The tails could be made hypoxic by tying rubber bands round the base of the tail and passing "white-spot" nitrogen through all holes in the disc, five minutes prior to and during the irradiation. The holes could also be flushed with 100 per cent oxygen, or the whole apparatus could be placed inside a polythene bag flushed with 100 per cent oxygen.

The rats were constrained in tubes of a simular design and arranged parallel to each other, three on a board. The tails passed through narrow Perspex tubes, also parallel to one another, and 3 mm lead was used to shield the bodies of the animals and the tails, apart from a 9 cm length in the mid-tail region. In this length, the central 3 cm received the nominal dose, and brass wedges at the sides reduced the dose to approximately 80 per cent, 65 per cent and 50 per cent of the nominal dose at 1, 2 and 3 cm respectively from both edges of the central 3 cm (see top of Fig. 2). A 3 cm nominal beam width was chosen, as tolerance doses in man rise dramatically at widths lower than this due to marked edge effects on healing. The field dose distribution shape was chosen so as to match approximately that produced by the neutron beam, described below.

Neutron irradiations

14–15 MeV neutrons were produced by the D-T reaction in a prototype Elliot Q-type tube, as described previously (Greene and Major, 1971). Steel plates in front of the target reduced the vertical primary beam to a width of 3 cm. Four rats were placed longitudinally inside the beam collimator, two on each side, with their tails nearest to the target and passing at right-angles to the body across the beam slit, through tapered holes in a Perspex block. Two 3 cm thick steel plates shielded the rat bodies. The arrangement of the four tails was such that two tails received about 10 per cent less dose than the other two (due to their greater distance from the target) and this enabled two dose groups to be irradiated simultaneously. The reduction in dose-rate across the tails was about 5 per cent, and this was corrected for in the single-dose and 2-fraction exposures by turning the animals and tails through 180 deg. halfway through the exposure, using the corresponding holes for the same dose. From 4 to 16 fractions this "turning-round" procedure was left to be random among dose fractions. The dose-rate to the tails was about 75 rad minute^{-1} and was measured with an ionization chamber described by Greene (1971). Doses include a γ-component of about 10 per cent, together with a similar percentage of low energy neutrons. The dose to the bodies of the rats was measured to be on average about 15 per cent of the tail dose, and this was higher at the rear (about 20 per cent) than at the head (about 10 per cent). The relative dose distribution along the irradiated length of the tail was as described in the previous section for X rays.

Skin reactions and necrosis

Early skin reactions were monitored twice weekly on an arbitrary reaction scale (Table I) based on a range of three units (1·0—erythema; 2·0—moist desquamation; 3·0—bleeding, loss of epidermis), with intermediate quarter points (cf. Fowler *et al.*, 1965). The scoring was continued until either the early reaction had healed (final score 0·5) or the animal was sacrificed due to a severe reaction which did not heal and which would have progressed to complete breakdown and necrosis of the irradiated portion and the distal tail. Initially, a time limit of ten weeks post-irradiation was taken for a measure of the proportion of tails which had not healed (the necrosis fraction). Retrospectively, it was found that about 4 per cent (9/204) of X-irradiated tails and about 8 per cent (9/111) of neutron-irradiated tails, which were scored as healed at ten weeks, had necrosed by six months post-irradiation. These late necroses were included in the necrosis fractions, but their exclusion does not change the results significantly. Dose-response curves for necrosis were analysed using standard probit methods, and regression lines were fitted using the computer programme described by Gilbert (1969) which provides values (with standard errors) for the ND_{50} (dose for 50 per cent necrosis) and the inverse slope (standard deviation of the distribution or the dose increment between ND_{16} and ND_{50}) of the probit line.

RESULTS

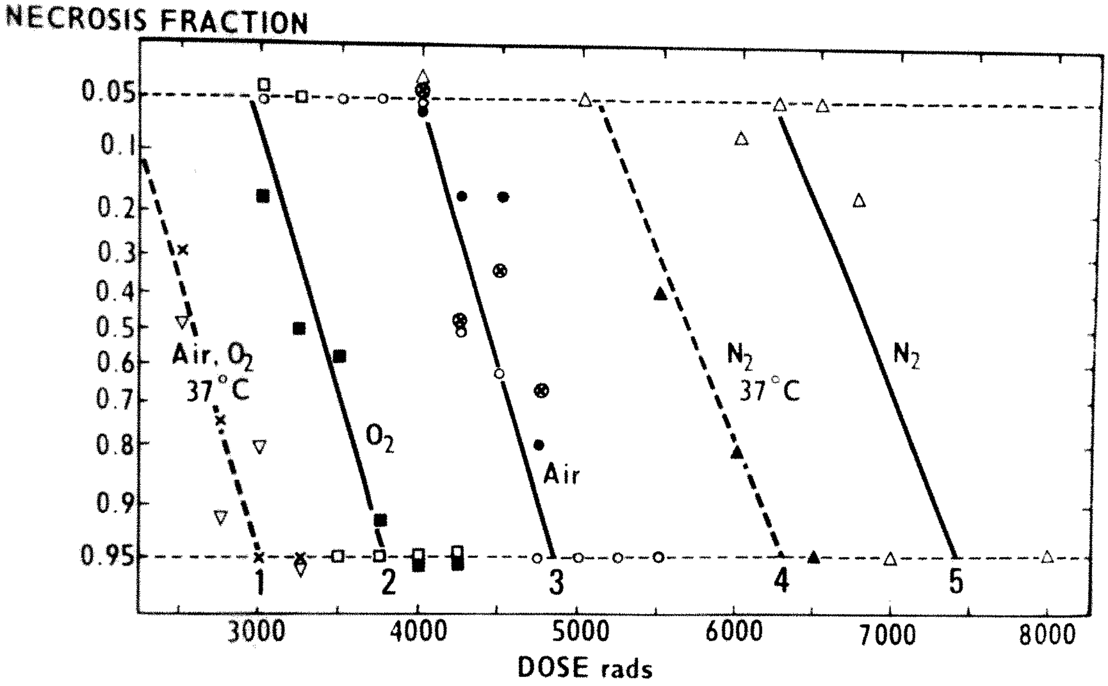
Effect of oxygenation and temperature on mouse tail necrosis from single X-ray doses

X-irradiation of mice breathing air at ambient temperature produced an ND_{50} of 4418 ± 42 rad (Fig. 1). This value is the mean of four independent experiments, and the pooled data for each dose are shown in the figure. Inter-experiment variation in ND_{50} was less than ± 5 per cent in these four experiments performed over a five-month period, and all the ND_{50} values presented are the mean of at least two experiments. The ND_{50} is not significantly affected by the addition of a whole-body dose equal to 5 or 10 per cent of the tail dose at each dose level (see line 3, Fig. 1).

TABLE I

Skin reactions

Reaction appearing		Reaction disappearing
0·5	Possibly different from normal	Almost normal
0·75	Slight erythema	Slight reddening persisting
1·0	Erythema	Reddening in healed epidermis
1·25	Erythema and skin flaking	Dry desquamation in small degree
1·5	Dry desquamation	Dry desquamation of scab in parts
1·75	Desquamation dry or moist in parts	Scab sloughing
2·0	Moist desquamation	Some of scab sloughing, sometimes desquamation persistent
2·25	Scab forming, moist in part	Scab smaller but persistent
2·5	Hard scab over whole or irradiated part	Hard scab persistent
3·0	Loss of epidermis, bleeding	Oedema in distal tail portion



Ambient temperature	37°C	Condition
○	X	Air
⊗	—	Air + 5% body dose
●	—	Air + 10% body dose
□	—	O_2 surrounding tail
■	▽	O_2 surrounding tail + O_2 breathing
△	▲	Clamp + N_2 surrounding tail

Fig. 1.

Mouse tail necrosis fractions after single doses of 290 kV X rays. Fractions of 0 or 1 shown at 0·05 or 0·95 levels respectively. Lines for 37°C shown dotted. Line numbers used in text.

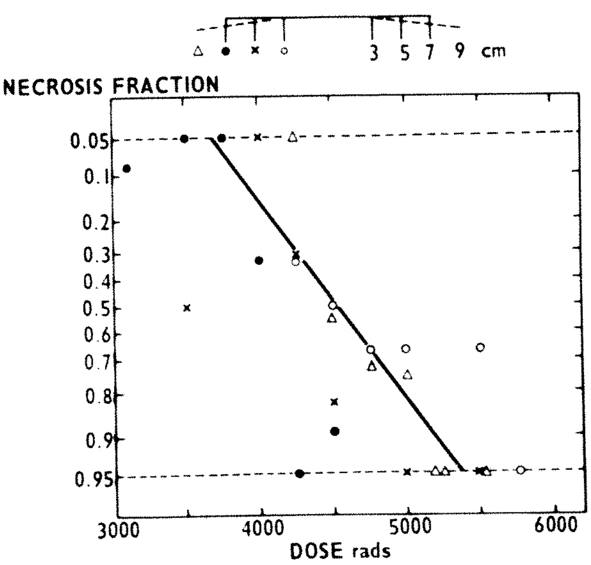


Fig. 2.

Effect of length of irradiated portion of rat tail on necrosis fraction, for single doses of 290 kV X rays. Line taken from Fig. 3 (single doses). Field dose distribution shown graphically at top of figure, with symbols corresponding to appropriate field widths.

For mice breathing air or oxygen at atmospheric pressure, but with their tails gassed with oxygen, the ND_{50} was 3,356±55 rad (line 2, Fig. 1).

For mice with severely-hypoxic tails, clamped and gassed with nitrogen, the ND_{50} was 6,818±158 rad (line 5, Fig. 1). Sensitivity was increased under all circumstances by raising the tail temperature to about 37°C (lines 1 and 4). This procedure reduced the above ND_{50} values to 6,000±133 rad (nitrogen), 2,662±88 rad (air), and 2,664±85 rad (oxygen). The air/oxygen differential was thus eliminated by this procedure. Also, the nitrogen/oxygen ratio of ND_{50} values was slightly increased from 2·03 to 2·25. For interest, the lowest value of ND_{10} (dose for 10 per cent necrosis) was estimated at 2,300 rad, and this occurred in air or in oxygen at 37°C (line 1).

Effect of length of irradiated rat tail on necrosis by single X-ray doses

The effect of changing the length of the irradiated section of rat tail is shown in Fig. 2. The line is taken from Fig. 3 (single doses). Calculated ND_{50} values are 4,568±271 rad (3 cm length), 4,549±136 rad (3 cm+"edges", see 9 cm field in Fig. 2, and X-irradiation section), 4,050±321 rad (5 cm), and 4,113±100 rad (7 cm). The data at 5 cm are rather scattered and inconclusive, but there is a slight trend towards an increased sensitivity for the longer lengths. ND_{50} values in air are very similar for rats (4,550±140 rad) or mice (4,418±42 rad), although the inverse probit slopes are somewhat steeper for mice (about 264 rad) than for rats (about 502 rad).

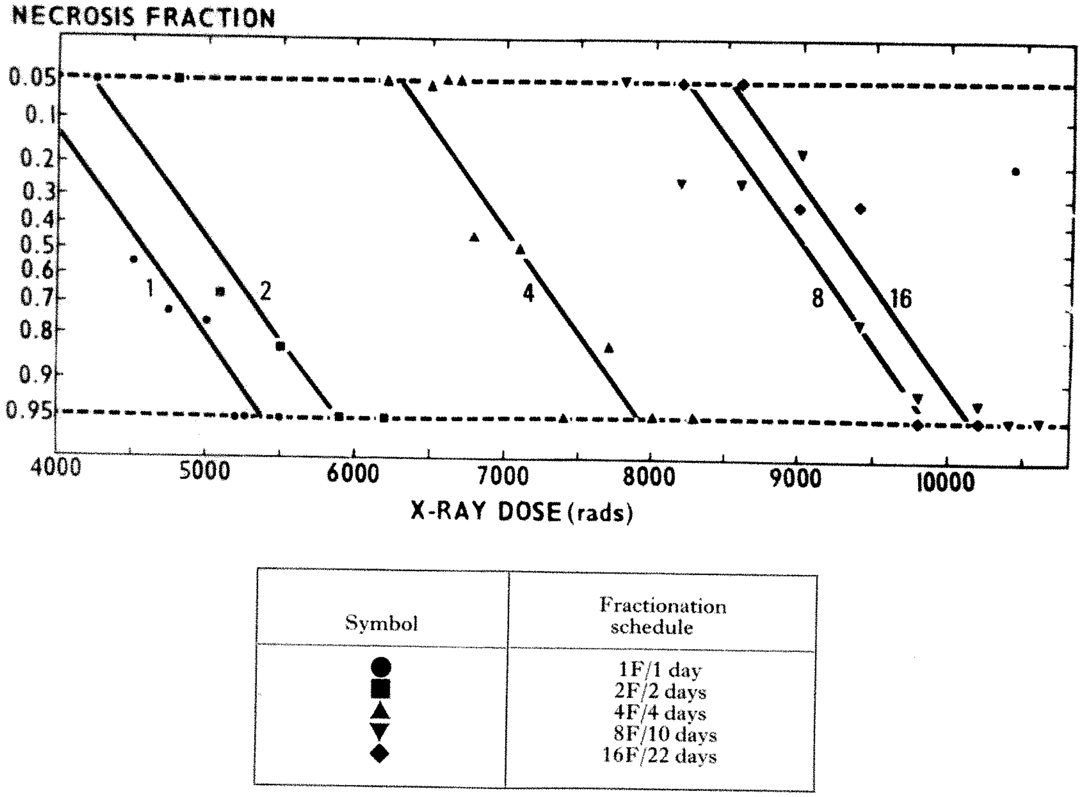
Fractionated X-ray or neutron doses

Dose-response curves for rat tail necrosis are shown respectively in Figs. 3 and 4 for fractionated X-ray and neutron doses. The inter-experiment variation was greater for the longer fractionation schedules, and again the values quoted are calculated from pooled data in at least two independent experiments for all cases except one (2 fractions of neutrons). The majority of preliminary data which were reported earlier (Hendry *et al.*, 1974) have been included. For clarity, necrosis fractions of 0 or 1 are shown on the dotted lines for the 0·05 and 0·95 levels respectively, and lines with a common probit slope (weighted mean from all fractionation schedules) are drawn through the data for all fractionation schedules with each radiation type. The calculated ND_{50} and probit slope values are shown in Table II for each fraction number. Also shown are ND_{10} values, estimated from the fitted lines. For interest, values in parentheses are those calculated for a common probit slope (irrespective of fractionation schedule, as drawn in Figs. 3 and 4 for clarity), and these values are similar to those for the individually fitted lines in every case. With X rays, an increase in total dose for a given level of necrosis is observed with an increase in the number of fractions, but with neutrons the increase is much reduced and is confined to the change from 1 to 2 fractions.

Iso-effect data for ND_{10} and ND_{50} are shown in Fig. 5 on a log/log plot, with total dose plotted against fraction number. Corresponding RBE values are shown in Table III, calculated from the parameter values given in Table II. For comparison with other published data, regression lines have been fitted to the data in Fig. 5, yielding slope exponents of 0·29 (ND_{50}) and 0·31 (ND_{10}) for X rays, and 0·06 (ND_{50}) and 0·07 (ND_{10}) for neutrons, although it is clear that the X-ray data are becoming less steep between 8 and 16 fractions, and, as noted above, there is no clear effect of dose fractionation between 2 and 16 fractions with neutrons.

Variation in skin reaction level with time after irradiation

Reaction levels at varying times after single doses of neutrons are shown in Fig. 6. Similar curves were obtained for all other dose schedules. The times to peak reaction and healing are shown in Table IV



Symbol	Fractionation schedule
●	1F/1 day
■	2F/2 days
▲	4F/4 days
▼	8F/10 days
◆	16F/22 days

Fig. 3.

Response of rat tails to daily fractionated doses of 290 kV X rays. Lines drawn according to parameters in parenthesis in Table II.

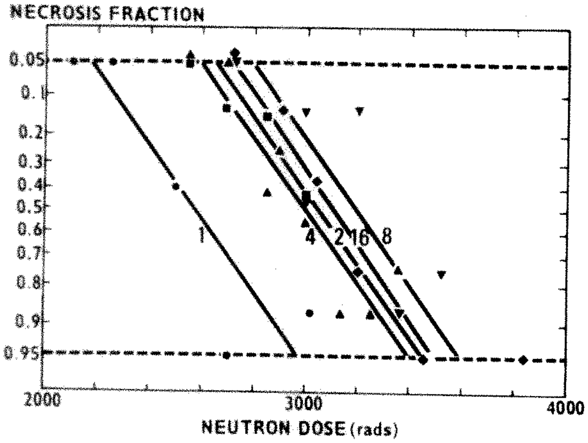


Fig. 4.

Response of rat tails to daily fractionated doses of 14 MeV neutrons. Symbols and lines as for Fig. 3.

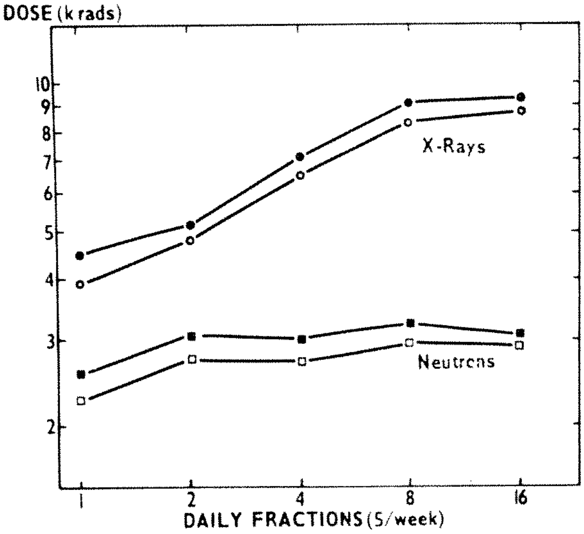
according to fraction number for X rays and neutrons. As expected, peak reactions occurred sooner after the end of the longer fractionation schedules, but taking all fractionation schedules together peak reactions and healing occurred on average only two and three days later after neutrons than after X rays.

"Average" reactions were also calculated from curves such as those shown in Fig. 6, as this endpoint has been used extensively in preference to peak reaction (Fowler *et al.*, 1965; Fowler *et al.*, 1974). The average reaction was calculated over the period from 16 to 60 days after single doses, *i.e.* twice the time limits used by Fowler *et al.* (1965) for mouse feet, in view of the longer reaction time course observed for this system. The start of the time period was advanced by the number of days (from the last day of the schedule) by which the initial rise in the reaction curve was advanced (cf. Fowler *et al.*, 1972). These values were nil days (2 F), three days (4 F), five days (8 F) and 14 days (16 F).

TABLE II
Parameters of Probit lines. Standard errors quoted

Daily fractions/Overall time	X rays (rad) ND$_{10}$*	X rays (rad) ND$_{50}$	X rays (rad) Slope	Neutrons (rad) ND$_{10}$*	Neutrons (rad) ND$_{50}$	Neutrons (rad) Slope
1F/1 day	3,900 ±260 (3,950)	4,550 ±140 (4,550)	509 ±171 (502)	2,290 ±110 (2,270)	2,570 ±80 (2,570)	219 ±80 (242)
2F/2 days	4,800 ±150 (4,420)	5,140 ±90 (5,070)	264 ±92 (502)	2,740 ±240 (2,740)	3,050 ±130 (3,050)	246 ±123 (242)
4F/4 days	6,570 ±130 (6,440)	7,040 ±80 (7,090)	368 ±80 (502)	2,670 ±90 (2,690)	2,980 ±50 (2,980)	237 ±67 (242)
8F/10 days	8,170 ±200 (8,440)	9,070 ±120 (9,080)	700 ±120 (502)	2,950 ±180 (2,890)	3,210 ±120 (3,200)	357 ±182 (242)
16F/22 days	8,880 ±170 (8,690)	9,320 ±110 (9,330)	342 ±103 (502)	2,900 ±70 (2,800)	3,090 ±40 (3,110)	147 ±45 (242)

*Estimated from fitted line.
Values in parentheses are those calculated for a common slope (irrespective of fractionation).



	ND$_{50}$	ND$_{10}$
X-rays	●	○
Neutrons	■	□

Fig. 5.

Iso-effect data from Table II shown on log/log plot.

For each fractionation schedule, peak and average reaction were each correlated with necrosis fraction, and the levels of peak or average reaction corresponding to a necrosis fraction of 0·5 are shown in Table V. This clearly demonstrates the similarity of the values for all fractionation schedules (1 to 16 fractions), indicating that any of the three endpoints can be used to predict the same effect of X-ray or neutron fractionation for this system, in terms of the slopes of the respective iso-effect curves. However, the peak reactions (but not the average reactions) for neutrons are slightly but consistently higher than those for X rays, as shown by the arithmetic mean of the values for all fractions (Mean 1, Table V). In view of the similarity in the reaction/necrosis correlation for all the fractionation schedules, a correlation was made for the combined data, irrespective of fractionation schedule. These relationships are shown in Fig. 7. Overall values were estimated (for the whole series of X-ray or neutron experiments) of the peak or average reactions for a necrosis fraction of 0·5 (Mean 2, Table V). A mean peak reaction of moist desquamation after X rays will heal in 50 per cent of tails. Peak reaction levels for X rays and neutrons are significantly different ($P < 0{\cdot}001$), whereas average reaction levels for the two radiation types are not significantly different ($P \sim 0{\cdot}1$).

TABLE III

Neutron RBE values for 10% and 50% necrosis with standard errors. Values in parentheses are those calculated for common probit slopes (irrespective of fractionation)

Daily fractions/ Overall time	RBE	
	ND_{10}	ND_{50}
1F/1 day	1·70 ±0·13 (1·74)	1·77 ±0·08 (1·77)
2F/2 days	1·75 ±0·16 (1·61)	1·69 ±0·08 (1·66)
4F/4 days	2·46 ±0·09 (2·39)	2·36 ±0·05 (2·38)
8F/10 days	2·77 ±0·20 (2·92)	2·83 ±0·09 (2·84)
16F/22 days	3·06 ±0·09 (3·10)	3·02 ±0·05 (3·00)

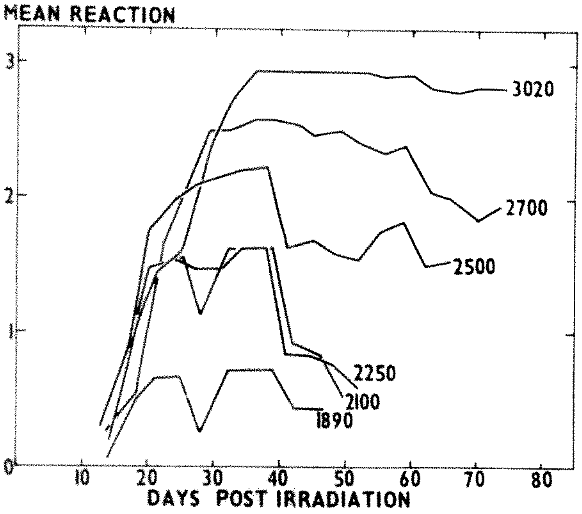


Fig. 6.

Reaction curves for 1 fraction of neutrons. Rad doses shown on curves. Reaction scale as in Table I.

TABLE IV

Times (after last fraction) to peak reaction and healing for fractionated X ray or neutron doses

	Mean time to peak reaction (days)		Mean time to healing (days)	
Fractions	X	N	X	N
1	28	27	50	49
2	23	27	44	56
4	22	24	39	58
8	17	21	49	43
16	13	12	41	32

Discussion

Tail necrosis

Early skin reactions in mouse tails were used by Mottram and Gray (1940) to determine the RBE of γ rays to orthovoltage X rays, and X-ray dose levels were comparable with those used in the present work. The endpoint of tail necrosis described here is considered to be a useful, objective, model system for deriving general radiotherapeutic principles for a normal tissue. Healing of the irradiated tail portion requires at least the regeneration of the surrounding epidermis and the presence of a functional blood supply.

The inverse slope (about 500 rad) of the necrosis probit curve for X-ray doses in air is of the same order as that which can be deduced from human data on complication rates (*e.g.* Stewart and Jackson, 1975). This parameter indicates the sensitivity of systems to changes in dose. If damage to a single critical cell population is invoked as being responsible for the production of necrosis, an estimate for the cell D_0 slope of about 420 rad can be calculated, using an approximate factor of 1·2 for the ratio probit slope/D_0 slope (Lange and Gilbert, 1968). This is larger than that calculated for the mouse data (about 215 rad), and this could be due in part to a greater inter-experiment variation with rats than with mice (as the necrosis fractions at each dose are pooled values from different experiments). If different cell populations are responsible for necrosis at different necrosis levels, this would also tend to modify the overall probit slope.

Whole-body irradiation, oxygenation and temperature

Neutron-irradiated rats received an average whole-body dose of 15 per cent of the tail dose *i.e.* about 386 rad at the single dose ND_{50} of 2,570 rad. In terms of, say, bone marrow damage, this corresponds to a dose of about 463 rad of X rays, using an RBE value of 1·2 at this dose level for these neutron and X-ray sources (Hendry, 1972). Such an X-ray dose corresponds to about 10 per cent of the ND_{50} value for X rays, and this percentage dose does not affect the necrosis fraction for mouse tails (Fig. 1). Modifications of the RBE values reported in this paper due to systemic effects of whole-body irradiation are therefore considered unlikely.

The ND_{50} ratios for nitrogen/air and nitrogen/oxygen are in the same range as those reported by Fowler *et al.* (1965) for skin reactions on mouse feet. The dose modifications produced by changes in oxygen status (Fig. 1) demonstrate that the cell population responsible for "healing" the irradiated tail either contains a proportion of anoxic but viable

TABLE V

PEAK AND AVERAGE REACTIONS FOR NECROSIS FRACTION OF 0·5

	Peak reaction		Average reaction	
Fractions	X	N	X	N
1 2 4 8 16	2·21±0·25 2·21±0·37 2·01±0·35 2·21±0·40 2·13±0·21	2·27±0·20 2·57±0·17 2·29±0·20 2·25±0·13 2·35±0·13	1·75±0·33 1·74±0·34 1·68±0·34 1·78±0·20 1·77±0·32	1·82±0·15 1·97±0·09 1·89±0·18 1·54±0·32 1·76±0·20
Mean 1	2·15±0·06	2·35±0·04	1·74±0·06	1·80±0·04
Mean 2 Significance level	2·10±0·06 ←P<	2·35±0·05 0·001→	1·69±0·06 ←P~	1·81±0·05 0·1→

Standard errors quoted on means; standard deviations for each fraction number:
Mean 1 – arithmetic mean of 1 to 16 fraction values.
Mean 2 – values from combined correlation (irrespective of fractionation, see text).

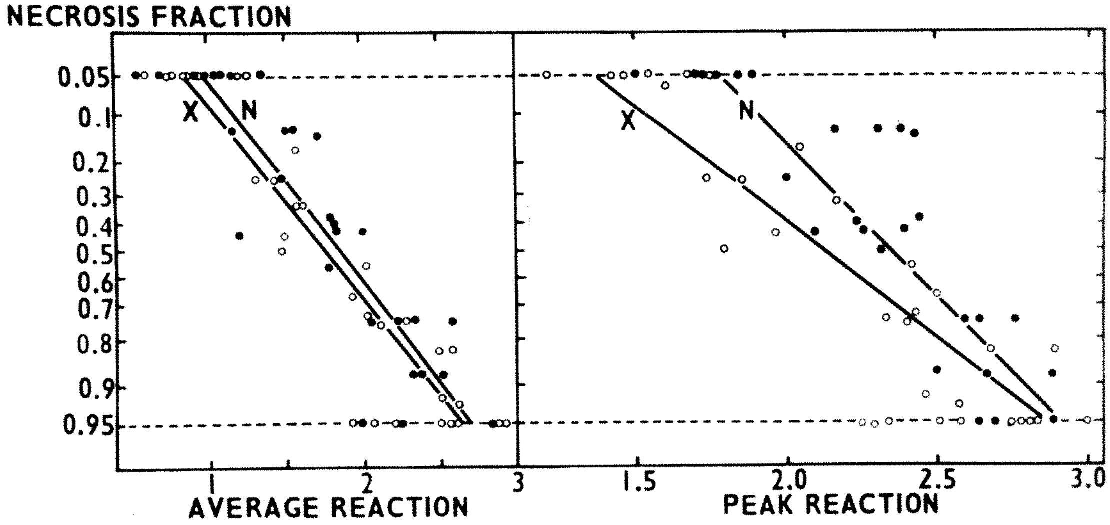


FIG. 7.

Correlation of necrosis fraction with peak or average reaction (all fraction data combined). Data at necrosis fractions of 0 or 1 shown at 0·05 or 0·95 levels respectively. ○, X rays: ● neutrons.

cells, or that it exists normally at a uniformly low oxygen tension. Field and Bewley (1974) demonstrated that the sensitive cells in rat foot skin were at a low oxygen tension, using the phenomenon of oxygen depletion at high dose rates. Also, the cells responsible for baby rat-tail stunting show a small but consistent O_2/air dose ratio for responses over a wide dose range (Dixon, 1967), which is indicative of a normal generalized hypoxia for this tissue. Nonetheless, the split-dose responses in air or in oxygen are similar for skin (Fowler *et al.*, 1965), or for tail stunting (Dixon, 1969), so the iso-effect curve slopes for better-oxygenated tissues than that described here are not expected to be modified by this effect. However, the RBE values (all fractions) may be slightly lower for better-oxygenated tissues (by about 12 per cent if the O_2/air differential is halved with neutrons, or by a maximum of 24 per cent if the differential is abolished).

X-irradiations of mouse tails at 37°C (about body core temperature) eliminates the air/oxygen differential seen in control mice, and this is presumably due to an increased oxygen availability from a better blood flow. A similar finding has been reported recently (Thrall *et al.*, 1975). However, the hypoxic (clamped in nitrogen) tails also become more sensitive on heating, indicating radioprotection afforded by the lower temperature of the normal rodent tail compared with that of the body. The increased sensitivity at the higher temperature is contrary to results recently reported by Brown *et al.* (1975), where doses for tail necrosis were higher at 37°C than at 20°C.

Early v. late damage

This study demonstrates that peak early reaction (about 30 days after single doses), average early reaction (16–60 days after single doses), or necrosis fraction (ten weeks to six months post-irradiation) all show the same effect of X-ray dose fractionation (1 to 16 daily fractions). Consequently, early reactions can predict necrosis rates over this range of fractions, for this system. This is similar to the conclusions reached by Field *et al.* (1967) for average early skin reactions and late deformity in rodents, but differs from those of Berry *et al.* (1974) for pig skin (over a larger range of fractions and time).

The above three endpoints are affected similarly by neutron fractionation. However, their quantitative inter-relationship differs slightly from that for X rays (Table V). This is compatible with the trend (not significant) towards less late rat foot deformity with neutrons than with X rays for a given average early skin reaction (Field, 1969), and slightly less late than early mouse foot skin reaction with helium ions than with X rays (Leith *et al.*, 1975). The use of peak early reaction as an endpoint in the estimate of RBE for necrosis would underestimate the neutron dose by about 10 per cent for all fractionation régimes with this tissue. "Average" reaction includes peak reaction and healing, so the above difference is expected to be less with this endpoint. Consideration of the X-ray and neutron dose distributions used in this work shows a probable 2–3 per cent lower neutron dose to soft tissue in the tail centre than to the tail surface. Also, the presence of bone in the tail may increase the absolute dose difference to certain structures, and this may account for some of the above 10 per cent difference—if tail healing does not depend solely on the damage which appears in skin macroscopically as the early reaction. Published work on tissues similar to those present in tail shows a slightly lower RBE (16 MeV D on Be cyclotron neutrons) for cartilage than for skin (reviewed by Field and Hornsey, 1971), and a similar RBE (D-T neutrons) for skin, spinal cord and capillary endothelium (reviewed by van de Kogel and Barendsen, 1974).

X-ray or neutron fractionation

The response of the tail to X-ray fractionation is similar to that for mouse feet (Fowler *et al.*, 1965; 1974), pig skin (Fowler *et al.*, 1963b) and human skin (reviewed by Fowler and Stern, 1963; Ellis 1968), namely a $(D_2–D_1)$ (difference of split-dose and single dose for same effect) of about 600 rad, and an iso-effect curve slope exponent of about 0·3 for daily fractionation. This is in spite of the higher absolute doses required to produce damage in this system. A similar conclusion was reached by Berry *et al.* (1974) for the higher tolerance levels for pig skin than for human skin.

The neutron data show an unusual effect, a $(D_2–D_1)$ of about 500 rad (only slightly lower than that for X rays), but no further effect of dose fractionation from 2 to 16 fractions. This effect is not observed for mouse intestine using the same neutron source (Hendry *et al.*, 1975) but it has been observed for mouse lung (Hornsey *et al.*, 1975) and intestine (Withers *et al.*, 1974) using cyclotron-produced neutron beams. The γ contamination of about 10 per cent in our work is insufficient to explain this effect, even if it is postulated that some cell death is produced by the γ-ray dose (250 rad) in the single neutron exposures, and that the γ-ray dose in the fractionated neutron exposures (less than 150 rad γ rays per fraction) has no effect.

The present data demonstrate that RBE values for tail tolerance (ND_{10}) rise from about 1·7 (single doses) to about 3·1 for a standard clinical-type three week (16F/22 days) dose fractionation schedule. The latter RBE value is expected to be 3·40±0·10 with respect to megavoltage X rays, using a conversion factor (megavoltage/300 kV) of 0·9 (Greene *et al.*, 1962). Better-oxygenated tissues may show a slightly lower RBE, and thus the above values are expected to be upper limits, *i.e.* calculated neutron doses will be "on the safe side". Neutron dose levels for necrosis are almost independent of fractionation from 2 to 16 fractions. This indicates that for the tail (and for the lung—Hornsey *et al.*, 1975) an RBE measurement for 2 fractions will provide neutron tolerance doses applicable up to 16 fractions.

The RBE values determined here are valid solely for rat tails. In view of the different neutron RBE values between tissue types (Field and Hornsey, 1971), these values should be used with caution when 14 MeV neutrons are used in clinical trials.

ACKNOWLEDGMENTS

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Effects of fractionated irradiation on mouse lung and a phenomenon of slow repair

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ABSTRACT

The LD/50 between 40 and 180 days after irradiation of the thorax has been taken as a measure of lung damage in mice. The method has been used to derive the relationship between total dose, number of fractions (N) and overall treatment time (T). For X rays the results fit an Ellis type of relationship, *i.e.* total dose $\propto N^{0\cdot 25}\ T^{0\cdot 07}$. This only applies for more than 8 fractions, below which $N^{0\cdot 39}$ becomes a good fit to the results. For neutrons, the best fit is total dose $\propto T^{0\cdot 07}$. Various possible explanations for the T factor are discussed, but for lung damage we attribute it to a slow repair process which possibly may only be observed in slowly proliferating tissues. Slow repair is about 100 times less rapid than Elkind-type of repair of sublethal damage and whereas Elkind repair is greatly reduced for irradiation with fast neutrons, relative to X rays, slow repair is not.

In radiotherapy both the overall treatment time and number of dose fractions are frequently altered in order to try to achieve the optimum therapeutic ratio. Normally the aim during this procedure is not to increase the damage to normal tissues. Therefore a knowledge of the relationship between total dose of X rays, overall treatment time and number of fractions is of major importance. With the increasing availability of fast neutrons it is also necessary to understand the relationship for high LET radiation as well as for X rays. Data from patients are difficult to obtain over a wide range of time, dose and number of fractions. However, animal experiments can be used to elucidate the principles involved which may give useful guidelines when clinical techniques are extended beyond normal practice.

Lung is frequently a limiting normal tissue in radiotherapy and it is important to understand the effects of radiation on this tissue. Ellis (1969) suggested a relationship of the form:

$$\text{Total dose} \propto N^{\alpha} T^{\beta}$$

for damage to connective tissues and we shall examine the relevance and possible implications of such a relationship for pulmonary damage in mice.

Phillips and Margolis (1972) suggested that after irradiation of the thorax alone, mice die within 30 days from damage to the oesophagus, and between 80 and 160 days from damage to the lungs. Wara *et al.* (1973) presented sufficient values of LD/50 for lung damage in mice, ranging from single doses up to 20 fractions given on five days per week, to construct a Strandqvist curve (Strandqvist, 1944) which had a slope of 0·44. A similar value, of 0·41, was obtained for damage to human lung from observations on radiotherapy patients. It was concluded that the factors which apply to man are similar to those in mice. Wara *et al.* (1973) were also able to make the distinction between overall treatment time and number of fractions from limited data on mice, and derived the formula total dose $\propto N^{0\cdot 38}\ T^{0\cdot 06}$, where N is the number of fractions given and T is the overall treatment time in days.

The LD/50 at six months is particularly useful for fractionation studies extending over several weeks because death normally occurs several months after irradiation, enabling a wide range of number of fractions and overall treatment times to be used. This is not the case for other tissues on which similar work has been done; for example, the radiation response of skin or intestine, in which reactions often have to be scored whilst a fractionated irradiation schedule is still in progress. This complicates the interpretation of results obtained from such early responses. In the work presented here we have measured the LD/50 (40 to 180 days) following total thoracic irradiation and have extended the data of Phillips and Margolis (1972) and Wara *et al.* (1973) on pulmonary damage by (a) giving a range of fractions, from 2 to 30 in a fixed overall treatment time of six weeks, and (b) giving either 2 or 5 fractions in a range of overall times from 24 hours to 54 days. Although most of the work was done with X rays, sufficient data were obtained with fast neutrons to draw conclusions regarding the response of mouse lung tissues to this high LET radiation.

The results are used to distinguish between the effects of overall treatment time and number of fractions. The sparing of damage associated with an increase in number of fractions is probably primarily dependent on the repair of sublethal damage between fractions. It was previously suggested that the sparing of damage by increasing overall treatment time may be due to repopulation of the tissue from surviving cells (Field and Hornsey, 1974) but it is now suggested that this sparing is due to a process of "slow repair" independent of cell repopulation and similar in some ways to the repair of sublethal damage.

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Experimental Techniques

Female TO mice, six weeks old, were irradiated either with 250 kV X rays, 7·5 MV X rays or with fast neutrons. They were anaesthetized with sodium pentobarbital at 65 mg per kg of mouse. During each irradiation the mice were breathing air at room temperature. Very few mice died after single doses of anaesthetic, and about 4 per cent for 30 doses. These low figures are probably partly due to the mice being allowed to recover from anaesthesia in a box warmed to 30°C. On average, there was no change in weight during the fractionated treatments.

Fractionation experiments were done in series, each accompanied by animal survival data for single doses. In this way it was possible to intercompare the results of each series.

The fast neutrons were obtained from the Medical Research Council's cyclotron at Hammersmith Hospital by bombarding a beryllium target with 16 MeV deuterons. The mean neutron energy was about 7·5 MeV and the beam contained about 3 per cent of γ rays. Mice were irradiated, eight at a time, with a dose-rate of about 70 rad/minute.

The 250 kV X rays were filtered with 0·25 mm Cu and 1 mm Al, giving a HVT of 1·3 mm Cu. Six mice were irradiated simultaneously in a jig rotating once every two seconds. Thus the mice were rotated through the field, which ensured delivery of the same dose to each mouse. Both the head and the body below the xiphisternum were shielded with lead, so that the whole thorax was irradiated. The dose-rate was 170 rad/minute. Further details of both the neutron and 250 kV X-irradiations are described by Field and Hornsey (1974).*

The 7·5 MV X rays were produced on the Medical Research Council's linear accelerator at Hammersmith Hospital. The irradiation procedure was similar to that used with 250 kV X rays except that eight mice were irradiated simultaneously and the lead shielding was increased to 7 cm thick. The whole body dose was less than 3 per cent of the dose to the thorax. 1 cm Perspex overlaid the thorax to ensure full secondary electron equilibrium. The dose-rate was about 100 rad/minute. The dosimetry was checked by lithium fluoride capsules implanted into the chests of dead mice, as well as with a small ionization chamber with the jig not rotating. The agreement between the methods was within ±2 per cent.

Results

Death between 40 and 180 days after irradiation of the thorax was used in a previous study of the effects of single and split doses of X rays and fast neutrons where it was shown that the pattern of death after neutrons was similar to that after X rays (Field and Hornsey, 1974). The same endpoint has been used in the present work.

A small number of mice died from causes other than lung damage before 80 days and a post-mortem examination was performed on as many of these as possible. In the high dose range (for which more than half the mice surviving 80 days died by 180 days) about 5 per cent of the total number irradiated died within ten days from damage to the intestinal tract. About 10 per cent more died between 10 and 30 days from damage to the oesophagus. For the lower doses, deaths before 100 days after irradiation were rare. After all doses there were no deaths between 40 and 80 days. Animals which died between 80 and 180 days showed obvious signs of respiratory failure and many post-mortem examinations were performed. Lungs were frequently wet, showing signs of extravascular leakage. Tests for bacterial infection were made and were almost always negative. There was no oesophageal damage at these later times and no obvious changes in the heart. There were no cases of paraplegia, implying no severe damage to the spinal cord (as expected, since damage to cord in mice occurs at higher dose levels than those used in these experiments). Histological examination of the lungs showed severe damage to the alveoli. There were areas of massive infiltration of cells into the alveolar spaces (presumably macrophages) and areas of consolidation. There were also signs of fibrin leakage, but no sign of the development of hyaline membrane. The air passages had normal epithelia and were not blocked. Since severe damage to tissues other than lung was not noted, we conclude that mice died between 80 and 180 days from radiation damage to their lungs. Phillips and Margolis (1972) came to a similar conclusion. After 180 days, the proportion of irradiated animals dying was similar to that for unirradiated animals, for at least the next three to four months.

After fractionated irradiations the mice died later than after single doses if the time of giving the first dose was taken as day zero. However, a good match with the single dose data was obtained by

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*The neutron doses quoted are for Hammersmith Dosimetry prior to January 1, 1975.

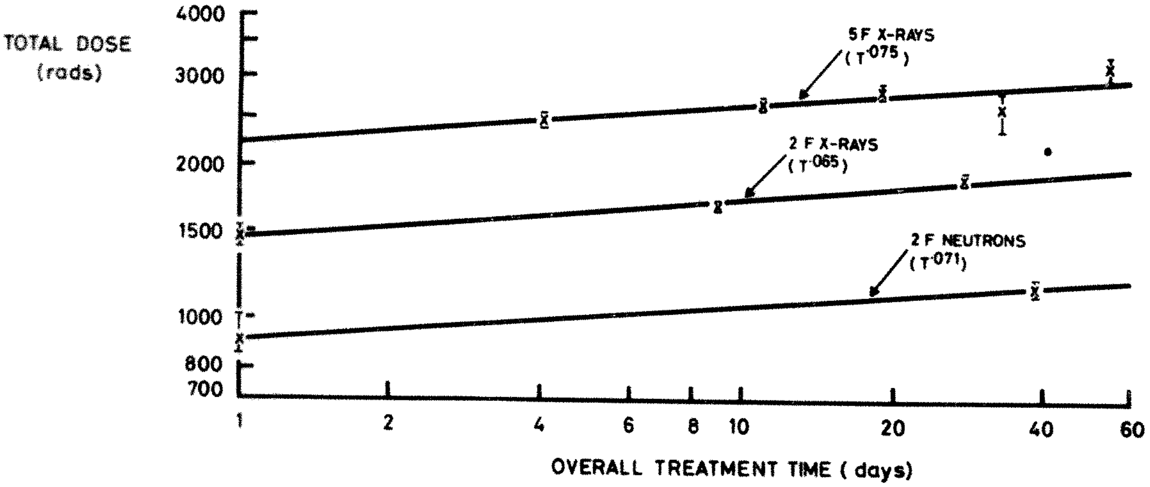

Fig. 1.

Log total dose as a function of log overall treatment time for 5 fractions and 2 fractions of X rays and 2 fractions of neutrons.

TABLE I

Values of LD/50, 40–180 days as a function of overall treatment time. Dose ranges given refer to 95 per cent confidence limits derived from probit analysis

2 fractions of 250 kV X rays (Expt. LX I)		5 fractions of 250 kV X rays (Expt. LX V)		2 fractions of neutrons (Expt. LN III)	
Overal treatment time (days)	LD/50	Overall treatment time (days)	LD/50	Overall treatment time (days)	LD/50
1	1,454 (1,386–1,520)	4	2,466 (2,422–2,537)	1	911 (610–1,036)
9	1,690 (1,619–1,762)	11	2,685 (2,605–2,763)	39	1,195 (1,167–1,225)
28	1,834 (1,739–1,931)	18	2,846 (2,745–2,950)		
		32	2,689 (2,368–2,832)		
		53	3,221 (3,018–3,388)		

using the middle time of the fractionated irradiations as day zero. The same pattern of response was observed after fractionated neutron and X-irradiation.

In the first series of experiments the overall treatment time was varied, whilst the number of fractions was constant. LD/50 values were obtained for 5 fractions and 2 fractions of 250 kV X rays and 2 fractions of fast neutrons, given in different intervals of time. The values are given in Table I. In Fig. 1 the logarithm of the total dose is plotted as a function of the logarithm of the overall treatment time for 5 and 2 fractions of X rays and 2 fractions of neutrons. Within the limits of experimental error the three lines are parallel with a slope of about 0·07. This is in good agreement with the value of 0·06 obtained by Wara *et al.*, 1973, using X rays and is the exponent of the T factor in the Ellis formula (Ellis, 1969). We may therefore use the factor $T^{0\cdot07}$ to estimate the total dose required in a given number of fractions, when the overall treatment time (T) is varied.

In the second series of experiments, the overall treatment time was kept constant whilst the number of fractions given in this time was varied. The following numbers of fractions were used: 4, 8, 15 or 30 fractions of 7·5 MV X rays, 8 and 30 fractions of 250 kV X rays, and 2, 4, 8 and 15 fractions of fast neutrons, all in six weeks. Also in these experiments the LD/50 for a single dose was obtained concurrently with each fractionation experiment. In order to relate the dose in N fractions (D_N) to the single dose (D_1) obtained concurrently, the effect of overall treatment time was removed by application of the factor $T^{0\cdot07}$. This effectively reduced the dose given

TABLE II

VALUES OF LD/50, 40–180 DAYS (WITH 95 PER CENT CONFIDENCE LIMITS) AS A FUNCTION OF NUMBER OF FRACTIONS. VARIOUS OVERALL TREATMENT TIMES ARE CORRECTED TO 1 DAY BY $T^{0\cdot07}$.

Treatment	Radiation	Expt. No.	LD/50	LD/50 corrected for overall treatment time by $T^{0\cdot07}$	$\frac{D_N}{D_1}$
S/D	250 kV X rays	LX III	1,317 (1,254–1,419)	1,317	1
8F/6W	250 kV X rays	LX III	3,872 (3,730–4,021)	2,996	2·27
30F/6W	250 kV X rays	LX III	5,063 (4,806–5,332)	3,918	2·97
S/D	7·5 MV X rays	LX8–I	1,293 (1,252–1,338)	1,293	1
4F/6W	7·5 MV X rays	LX8–I	2,944 (2,821–3,064)	2,278	1·76
8F/6W	7·5 MV X rays	LX8–I	3,597 (3,444–3,750)	2,783	2·15
15F/6W	7·5 MV X rays	LX8–I	4,376 (4,161–4,588)	3,386	2·62
30F/6W	7·5 MV X rays	LX8–I	5,180 (4,938–5,432)	4,008	3·10
S/D	Fast neutrons	LN III	808 (738–876)	808	1·0
2F/6W	Fast neutrons	LN III	1,195 (1,167–1,225)	925	1·14
4F/6W	Fast neutrons	LN III	1,193 (1,117–1,280)	923	1·14
8F/6W	Fast neutrons	LN III	1,269 (1,116–1,538)	982	1·22
15F/6W	Fast neutrons	LN III	1,163 (849–1,409)	900	1·11
S/D	250 kV X rays	LX I	1,078 (1,025–1,131)	1,078	1
2F/1d	250 kV X rays	LX I	1,454 (1,386–1,520)	1,454	
2F/9d	250 kV X rays	LX I	1,690 (1,618–1,762)	1,449	
2F/28d	250 kV X rays	LX I	1,834 (1,739–1,931)	1,452	
				Av. 1,452	1·35
S/D	250 kV X rays	LX II	1,234 (1,172–1,335)	1,234	1
2F/1d	250 kV X rays	LX II	1,539 (1,499–1,607)	1,539	1·25
S/D	250 kV X rays	LX V	1,167	1,167	1·0
5F/4d	250 kV X rays	LX V	2,466	2,238	
5F/11d	250 kV X rays	LX V	2,685	2,270	
5F/18d	250 kV X rays	LX V	2,846	2,325	
5F/32d	250 kV X rays	LX V	2,689	2,110	
5F/53d	250 kV X rays	LX V	3,221	2,439	
				Av. 2,276	1·95
S/D	300 kV X rays	Wara *et al.* 1973	1,324	1,324	1
2F/1d	300 kV X rays	Wara *et al.*	1,698	1,694	1·28
4F/3d	300 kV X rays	Wara *et al.*	2,318	2,146	1·62
10F/11d	300 kV X rays	Wara *et al.*	3,694	3,123	2·36
10F/25d	300 kV X rays	Wara *et al.*	3,873	3,092	2·34
20F/25d	300 kV X rays	Wara *et al.*	4,668	3,726	2·81

in N fractions in T days to N fractions in one day. Most data for this analysis were obtained for an overall time of six weeks, for which the time correction factor was the same in all cases; however, the same method was used for 5 fractions and 2 fractions in various overall times. In addition the results of Wara *et al.* (1973) were similarly normalized. Full details of the experimentally obtained values and applied corrections are given in Table II, and the results are shown graphically in Fig. 2, where the logarithm of D_N/D_1 is shown as a function of the logarithm of the number of fractions (N). The slopes of the curves for neutrons and X rays in Fig. 2 are the exponents of the N factors for neutrons and X

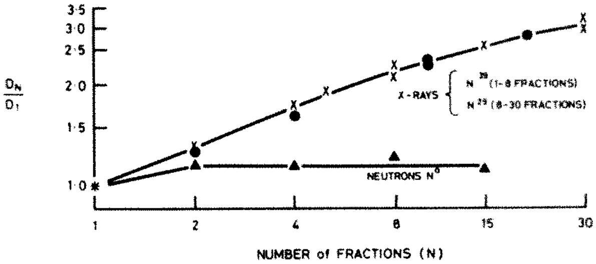

FIG. 2.

Log total dose as a function of log number of fractions (see Table II).

X present X-ray results.

● results from Wara *et al.* (1973) for X rays

▲ present neutron results.

rays in a formula of the Ellis type. For neutrons, no difference in LD/50 was observed from 2 to 15 fractions, giving N^0 for more than 2 fractions. For X rays, the curve was probably continuously bending, but can reasonably be described by two straight lines, giving $N^{0 \cdot 39}$ from 1 to 8 fractions and $N^{0 \cdot 25}$ from 8 to 30 fractions.

Discussion

After irradiation of the thorax, mice die between 80 and 180 days later from damage to their lungs. However, the mechanism of radiation damage in the lungs of mice leading to death has not been established. Phillips (1966) has suggested, from electron microscopic studies, that the primary injury is to the vascular endothelial cells, leading to plasma cell, mast cell and fibroblast infiltration and ultimately to capillary occlusion. Kurohara and Casarett (1972), from a study in rats, concluded that death after irradiation of the thorax was due to pneumonic infection superimposed on developing pulmonary fibrosis. Maisin (1970) concluded from experiments with mice that radiation pneumonitis was due both to direct radiation damage to parenchymal cells and to indirect damage, secondary to injury to the vascular connective tissue. Van den Brenk (1971) has suggested that the primary damage might be to the alveolar epithelial cells, some of which are vacuolated and others not. It is thought that the vacuolated alveolar cells produce surfactant (Kikkawa *et al.*, 1975), a phospholipid which has special surface tension properties and prevents collapse of the alveoli on expiration. Loss of surfactant would also cause a change in the osmotic and hydrostatic balance which would result in exudation of plasma or blood into the alveolar spaces, a characteristic of radiation pneumonitis. At the present time the relative importance of these possible modes of pulmonary damage by radiation is not known.

The N factor

The relationship between the total dose required to produce a given level of damage and the number of fractions used must depend on the efficiency of cell killing as a function of dose, *i.e.* on the shape of the cell-survival curve and the ability to recover from sublethal damage between fractions. For skin damage in mice, Field *et al.* (1975) showed that the Ellis formula was a reasonable approximation to experimental results over the therapy dose range from 4 to 30 fractions. Beyond this range there may be deviations from this simple relationship (Douglas and Fowler, 1975). For the present lung results (Fig. 2), $N^{0 \cdot 25}$ is a good fit to the data for X rays from 8 to 30 fractions, and $N^{0 \cdot 39}$ from 1 to 8 fractions. For neutrons, the LD/50 is increased when a single dose is split into 2 fractions, but there is no significant difference when 2 fractions are increased to 15 fractions given in the same overall treatment time, *i.e.* N^0 is a good approximation. This is not significantly different from $N^{0 \cdot 04}$ derived for skin damage (Field, 1972).

The T factor

Whereas the sparing obtained by increased fractionation of dose (the N factor) is attributed to the recovery from sublethal damage, the sparing obtained by increasing the time of the fractionated treatment has not been clearly attributed to known events. In tissues with a rapid cell turnover the most significant factor is the rapid cellular repopulation, which in skin is a complicated function of time between fractions (Denekamp, 1973). It can, however, be equivalent to as much as 100 rad/day. In lung, which is a tissue with a much slower cell turnover, Field and Hornsey (1974) found an increase of 8 rad/day was necessary to give the same level of pneumonitis in split dose treatments and they suggested that this low level of dose increment might be due to a slow repopulation rate. Wara *et al.* (1973) suggested a factor of $T^{0 \cdot 06}$ for mouse lung, but this was based on rather limited data.

It became possible to derive a time factor for mouse lung damage from a much wider range of data, and independent of the number of fractions, by effectively reducing all fractionation schemes to the equivalent of two doses. This was achieved by reference to the relationship between total dose and number of fractions (Fig. 2). For example, with 5 fractions in 18 days, 2,846 rad is required to kill 50 per cent of the mice. From Fig. 2 the ratio of doses in 5 and 2 fractions to produce the same effect is 1·42. Thus 2,846 is divided by 1·42 to give an equivalent dose in two fractions of 2,010 rad. This value is plotted against 18 days in Figs. 3 and 4. All the available data from our own experiments and from Wara *et al.* (1973) were treated in this way to derive the data points in Figs. 3 and 4. The curves drawn are $T^{0 \cdot 07}$, normalized to 2 fractions in 24 hours in both cases and are a good fit to all the experimental data. Thus the curves for the N factor (Fig. 2) and T factor (Figs. 3 and 4) describe all fractionation régimes.

There are various possible explanations for the increase in total dose required to produce an LD/50 with increasing overall treatment time as seen in Figs. 3 and 4. These include:

(1) repopulation by surviving lung cells;

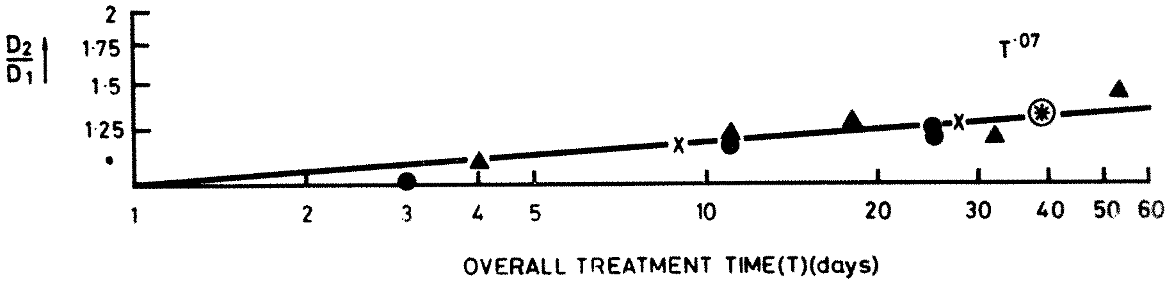

Fig. 3.

Log ratio of dose in two fractions (or effective dose in 2 fractions) to single dose as a function of log overall treatment time.

X present results for 2 fractions of X rays
▲ present results for 5 fractions of X rays (corrected to 2 from Fig. 2; see text).
● results from Wara *et al.* (1973) (corrected for N from Fig. 2).
★ two fraction neutron result.

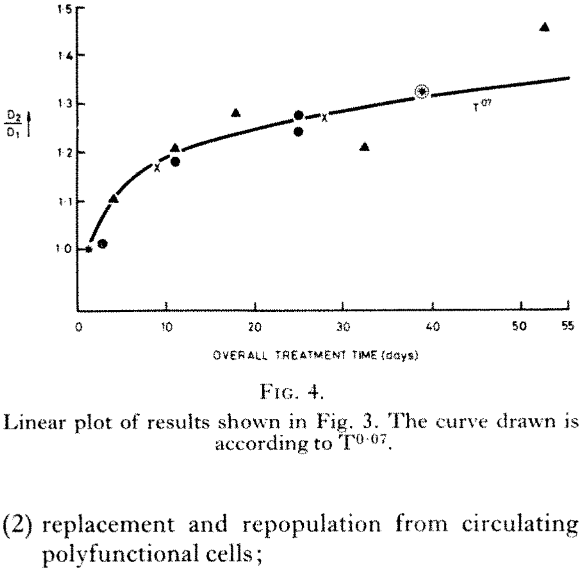

Fig. 4.

Linear plot of results shown in Fig. 3. The curve drawn is according to $T^{0\cdot07}$.

(2) replacement and repopulation from circulating polyfunctional cells;
(3) changes in sensitivity due to cell synchrony;
(4) changes in sensitivity due to induced or impaired intracellular repair mechanisms;
(5) some other slow repair process, hitherto undefined.

1. *Repopulation*

Lung is a highly organized tissue. It has many cell components which in general have slower turnovers than the stem cells of those tissues which show an immediate and acute response, for example the skin and gut. This slower cell turnover is consistent with a rather slow development of tissue damage. The most likely primary targets are endothelial cells or vacuolated alveolar cells. The latter have a turnover time of about a month (Bertalanffy and Leblond, 1953; Spenser and Shorter, 1962). With endothelial cells, estimates of labelling index with tritiated thymidine range from 0·1 to 1 per cent (Tannoch and Hayashi, 1972; Shimkin *et al.*, 1969), and no stimulation of capillary endothelial cell turnover has been observed until 40–70 days after irradiation (Fajardo and Stewart, 1971). In contrast, an increase in proliferation is stimulated within two or three days in gut (Lesher and Bauman, 1969; Withers and Elkind, 1970) and within about two weeks in skin (Denekamp, 1973). This is presumably a homeostatic response to cell death, which occurs soon after irradiation of these rapidly proliferating tissues. If cell proliferation were to account for the increase in total dose required as the time between fractions is increased, then in tissues with a low proliferation rate we would expect very little increase in the total dose required to produce a given level of damage until the interval between fractions was long enough for the damage to register and stimulate the proliferation rate. Only when this occurred would the total dose required to produce a given level of damage increase. In lung this was not the case; the increase occurred within a few days, and by ten days was more than half of that seen in 50 days. Repopulation, therefore, seems unlikely to be the cause.

2. *Repopulation from circulating polyfunctional cells*

It has been suggested to us that there may be circulating polyfunctional cells which may settle in damaged areas and provide a nucleus of cells for repopulation from outside the radiation field. So far as we are aware there is no evidence which demonstrates the existence of such cells. However, if such cells did exist then the stimulus to settle and repair damaged sites would presumably be the development of tissue damage. The development of tissue damage, as has already been discussed, is dependent on the life span of the limiting cells and therefore the repopulation and repair of tissue damage would follow a similar time course to that expected from endogeneous lung cells. By the same argument that repopulation from surviving endogenous lung cells is unlikely as the explanation for the T factor, we reject repopulation from circulating polyfunctional cells as a likely explanation.

3. *Effects of cell synchrony*

Cells in the more sensitive stages of the cell cycle will be killed in proportionately greater numbers than those in resistant phases, and this will induce some synchrony of cycle. If the surviving cells remained in the less sensitive phase of the cell cycle or progressed into a more sensitive phase then the population would initially become more resistant to the next fraction, not less, as is seen to occur (Figs. 3 and 4). Also, where such synchrony has been induced, cyclic changes in sensitivity are observed depending on the progression of the cells through their mitotic cycle. No such cyclic changes have been observed in our experiments on mouse lung (Fig. 4). It would be expected that the degree of synchrony and the radiation induced delay in progression would differ for different fraction sizes. If the sparing of damage were due to a fortunate combination of cell progression, it would not be the same for all fraction sizes. The proportionate increase in total dose required to compensate for an increase in overall treatment time was the same for both 2 and 5 fractions of X rays and also for 2 fractions of neutrons when the N factor was taken into account. It therefore seems unlikely that cell synchrony can be responsible for the T factor.

4. *Changes in cell sensitivity*

Two types of induced resistance to radiation have been observed. The first is that after a priming dose there is a change in slope of a second dose survival curve (Hillova and Drasil, 1967; Lockhart *et al.*, 1961), and the second is that there is additional accumulation of sublethal damage during a second dose (Horsley and Laszlo, 1971; Howard, 1975). If these effects increased throughout a multifraction treatment, either could explain the above observations on lung.

5. "*Slow Repair*"

It is possible that the effect is due to a slow repair process, analogous to "Elkind" repair of sublethal damage but taking about 100 times longer. If it were stopped by cell division, it would not be observed in rapidly dividing tissues, but only in slowly proliferating ones such as lung, kidney, liver, etc. The question then arises whether "slow repair" is simply a continuation of prompt "Elkind" repair and is due to the same basic process. Evidence that this is not so comes from the fact that recovery from "Elkind" repair of sublethal damage at 24 hours was less for neutrons than for X rays by about one-half (Field and Hornsey, 1974). In contrast, the only neutron result available for slow repair, *i.e.* at 39 days, shows that it occurs to the same extent as for X rays (Figs. 3 and 4). Thus slow repair is very similar after X rays or neutrons, whereas prompt repair (Elkind type) is not.

Slow tissue repair has been observed elsewhere *e.g.* in callus formation after a fracture (Hayashi and Suit, 1971) and in the disappearance in chromosome aberrations after irradiation of the liver (Curtis, 1967). This latter observation could be accounted for by the death and subsequent loss of those cells, but slow repair is an alternative hypothesis. It did not, however, appear to occur after irradiation of the liver with neutrons, whereas the "slow repair" reported here for lung damage seems to be the same for X rays and fast neutrons.

Various types of repair process have now been observed after irradiation. Repair of potentially lethal damage, *i.e.* damage which is influenced by the post-irradiation conditions of the cells (Whitmore and Gulyas, 1967), has been observed in various cell and tissue systems and has a similar time course to that of Elkind repair (Hahn and Little, 1972). Whether these two types of repair process are related is not known. A form of repair of potentially lethal damage has been described by Reinhold and Buisman (1975) and by Van den Brenk *et al.* (1974). Both of these groups of workers measured the repair which takes place between irradiation of the vascular system and the application of a proliferative stimulus. Both investigations showed that the vascular system has a considerable ability to repair damage in the weeks following irradiation. The experiments reported here are of a different nature, namely measurements of the additional dose requirred to compensate for increasing the time interval between two doses of radiation, but the time course is similar and "slow repair" may be related to the type of repair observed by Reinhold and Buisman (1973) and Van den Brenk *et al.* (1975).

CONCLUSIONS

1. The relationship between total dose, number of fractions (N) and overall treatment time (T) in causing the death of mice after irradiation of the thorax has been established. For both X rays and fast neutrons the time factor is $T^{0\cdot07}$ and is independent of the number of fractions given. For X rays the N factor is $N^{0\cdot39}$ from 1 to 8 fractions and $N^{0\cdot25}$ from 8 to 30 fractions. For neutrons no extra dose is required as the number of fractions is increased from 2 to 15.

2. A "slow type" of repair occurs in lung, which may have a different mechanism from the rapid (Elkind-type) repair of sublethal damage. Such a slow repair process could account for the T factor in radiotherapy for slowly dividing tissues. For rapidly dividing tissues repopulation probably accounts for the T factor and in such cases it is not possible to elicit slow repair.

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Modification of the radiocurability of a syngeneic murine squamous carcinoma by its site of growth, by electron-affinic drugs, and by ICRF 159

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ABSTRACT

A series of TCD_{50} experiments using a spontaneously arising, syngeneically transplanted, murine squamous carcinoma is reported. Tumours implanted intradermally and irradiated while they remained superficial had a small but nonetheless cure-limiting hypoxic fraction of cells (TCD_{50} 3,324–4,257 rad). The hypoxic fraction increased dramatically when these tumours invaded the subcutaneous tissues, or when tumours were implanted subcutaneously ($TCD_{50} > 5,544$ rad). Pre-treatment of mice with the electron-affinic drug Ro–07–0582 at a dose of 1 mg/g i.p. 20–30 minutes before irradiation effectively eliminated the hypoxic element from superficial tumours (TCD_{50} 1,862 rad). The same drug at a dose of 0·25 mg/g reduced the TCD_{50} for superficial tumours by a factor of 1·87 (3,986–2,134 rad), while another electron affinic drug, metronidazole, given at a dose of 0·25 mg/g, reduced the TCD_{50} by a factor of 1·28 (4,257–3,337 rad). Treatment of mice with the drug ICRF 159, 30 μg/g daily from the time of tumour cell injection until the day of irradiation, reduced the TCD_{50} in unclamped tumours by $>1·19$. However, a commensurate reduction of TCD_{50} in clamped tumours suggested that improved tumour vascularization could not explain fully the drug's "radiosensitizing" action. The unique single radiation dose curability of most human skin cancers is discussed in the light of the experimental results, and the possible clinical implication of an increase in hypoxic fraction with tumour invasion is raised.

It is a commonly accepted tenet of clinical radiotherapy that tumour cure is limited by the radioresistance of a sub-population of hypoxic but viable tumour cells. While such hypoxic cells may readily be demonstrated in experimental tumour systems (Kallman, 1972), their existence in human tumours remains inferential. Simple calculations based on representative radiation survival-curve parameters indicate that with the radiation dose levels employed clinically, tumour cure could never be achieved without one or more of the following assumptions:

(1) there are very few, if any, hypoxic clonogenic cells in curable tumours;
(2) complete reoxygenation of hypoxic cells occurs during the course of therapy;
(3) the radiation survival characteristics of human tumour cells are markedly different from those of other mammalian systems;
(4) only a very small proportion of the total cell population in curable tumours is clonogenic;
(5) some form of "host resistance" contributes independently to tumour cell killing.

The most plausible of these assumptions, based on experimental evidence, is that reoxygenation occurs. Reoxygenation was first demonstrated by Van Putten and Kallman (1968), and Fowler *et al.* (1974) have shown that with a knowledge of the time scale of reoxygenation in an experimental system, fractionation régimes can be optimized to produce the greatest "therapeutic gain". Reoxygenation cannot, however, account for the unique curability of most human skin carcinomas with *single* doses of radiation of the order of 2,000 rad, and the experiments reported here were designed to test whether the site of tumour growth might affect radiocurability—specifically, whether the hypoxic fraction of cells in an experimental tumour implanted into the skin might differ from that in the same tumour implanted or invading subcutaneously. In addition, experiments are reported in which the electron-affinic drugs Ro–07–0582 and metronidazole, and the "angiomorphic" drug ICRF 159, were used in attempts to reduce the hypoxic fraction of tumours.

MATERIALS AND METHODS

Mice and tumour

Female mice of the inbred albino strain WHT/Ht were used throughout these experiments. The tumour, designated Sq. Ca. "G", arose spontaneously in the forestomach of a female mouse of the WHT/Ht strain in October, 1970, and has since been maintained by serial subcutaneous transplantation and by storage in liquid N_2. Histologically, the tumour is a squamous cell carcinoma which showed extensive keratinization early in its transplant history; but for the greater part of the duration of the experiments described in this paper

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(representing passage numbers 74–108), it has been less well differentiated, though readily recognizable as a squamous carcinoma.

Quantitative transplantation assays of the tumour by the subcutaneous route show a TD_{50} (number of viable tumour cells required to achieve 50 per cent "takes") of 200–300 cells when viable cells were injected alone, and four to eight cells when viable cells were injected in association with an excess of lethally irradiated (LI) cells. The transplantation kinetics of the tumour are consistent with single-cell transplantation when excess LI cells are admixed, but are "anomalous" (Porter *et al.*, 1973) when viable cells are injected alone, *i.e.* upwards of 10^4 cells are required for 100 per cent successful transplantation. In both circumstances, the median latent period between injection of cells and the formation of palpable tumours is inversely correlated with the logarithm of the number of viable cells injected.

Intracutaneous tumours for TCD_{50} (dose for 50 per cent cures) experiments were produced by injection of 0·01 ml. of a cell suspension containing about 10^5 cells into the superficial dermis. For these injections, a dissecting loupe was used to place a 27-gauge needle accurately into the dermis. Correct placement was indicated by resistance to injection, and the formation of a blanched zone over the bleb with exaggerated prominence of skin rugae. Histological examination of sites immediately after injection showed the cells to be located in the reticular dermis. From such inocula, tumours grew as flattened plaques in the skin with elevated, rolled margins and subsequent central ulceration (Fig. 1). Such tumours provided a reasonable gross and microscopic facsimile of a human squamous carcinoma.

TCD_{50} experiments were performed on three classes of tumour:

(1) small tumours of 5–6 mm diameter × 1–2 mm thick in which growth remained superficial;

(2) more advanced tumours of 7–9 mm diameter × 3–4 mm thick in which deep invasion had occurred;

(3) tumours resulting from direct subcutaneous injection of tumour cells, which were irradiated on reaching a mean diameter of 6–7 mm.

Irradiations

Local tumour irradiations were performed, four at a time, using a Westinghouse X-ray machine (250 kV; 15 mA; 1·3 mm Cu HVT; 494 rad/minute). Mice were lightly sedated with tribromethanol (Avertin), 150 mg/kg s.c., but remained fully conscious and rousable during irradiation. They were placed in individual lead boxes which had been specifically constructed to allow the flap of skin bearing the tumour (on the left flank) to be drawn out from the box onto a Perspex stage during the irradiation. The skin flap was loosely tethered to a central pillar to prevent retraction during irradiation, but care was taken to avoid tension which could have compromised blood flow.

For irradiations under hypoxic conditions, a screw-down metal clamp was applied across the base of the skin fold bearing the tumour, five minutes before and during the irradiations. All clamps were left applied for the same length of time, irrespective of the duration of radiation exposure.

Calculation of TCD_{50} values

TCD_{50} assays were performed using groups of five to nine mice for each radiation dose level. Animals were examined thrice weekly for evidence of local recurrence which, when it occurred, was evident within 30 days in 75 per cent of cases. All mice were kept for 100 days unless they developed recurrence or died of metastatic disease. For the purpose of analysis, mice which died from metastases with their tumour sites clear later than 30 days were scored as "provisional cures", while those which died earlier were excluded from the data. This approach was used to avoid being left with too few mice per group for satisfactory analysis. The actual number of mice in each assay in the "provisional cure" category is given with the results,

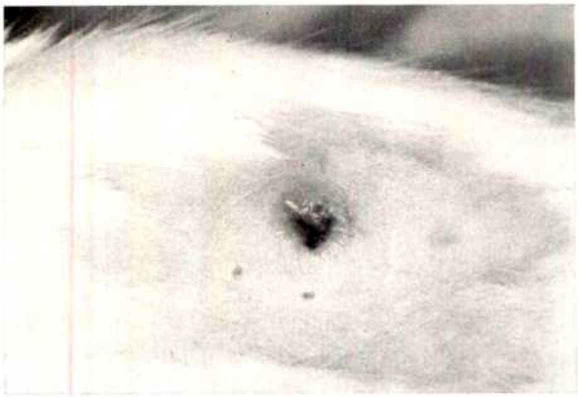

Fig. 1.

Close-up photograph of a lesion produced by injecting 10^5 cells of WHT Sq. Ca. "G" into the dermis of a syngeneic mouse six days earlier. The marker spots are 5 mm apart, and the lesion is 1–2 mm thick. The macroscopic similarity between this type of lesion and primary squamous carcinomata of the skin in humans is apparent.

while the effect of their inclusion on the interpretation of the data is considered in the "Discussion" of this paper. With this system, there were no cases of ambiguous recurrences, as defined by Fowler *et al.* (1974), since all recurrent tumours grew progressively.

Estimates of TCD_{50} values were made using a computer program. Briefly, the program is based on the biological premise that tumour recurrence depends on the Poisson probability of one or more clonogenic units surviving the test dose of irradiation. The slope of the tumour control curve is theoretically dependent on the radiosensitivity of the most resistant subpopulation of tumour cells, which must be entered into the program, along with cure data.[*] The program produces, by the method of maximum likelihood, estimates of TCD_{50}, the standard error of TCD_{50} and χ^2 for goodness of fit to the slope specified.

Determination of radiation survival parameters for hypoxic cells

Mice bearing subcutaneously transplanted tumours were killed by neck fracture, and after five minutes were exposed to graded doses of whole-body irradiation using a ^{60}Co source. Radiation dose levels of 1,200–6,000 rad were employed. After irradiation, the tumours were excised aseptically, and single-cell suspensions were made using the methods of Hewitt (1966). Transplantation assays were then performed using appropriate cell dilutions. Twelve to 16 sites were injected with each cell dilution. Sufficient lethally irradiated tumour cells were added to all inocula to maximize the Révész effect. For each radiation dose tested, the TD_{50}, *i.e.* number of apparently viable cells required for 50 per cent tumour takes, was computed as previously described (Porter *et al.*, 1973). By relating this TD_{50} to unirradiated control values, the surviving fraction for each radiation dose could be obtained.

Drugs

Experiments were performed using the following drugs:

(1) 1-(2-nitro-1-imidazolyl)-3-methoxy-2-propanol (Ro–07–0528) kindly supplied by Roche Products, Ltd.;

(2) 2-methyl-5-nitroimidazole-1-ethanol (metronidazole or Flagyl) kindly supplied by May and Baker, Ltd.;

(3) (±)-1,2-bis (3,5-dioxopiperazin-1-yl) propane (ICRF 159) kindly supplied by the Imperial Cancer Research Fund.

Ro–07–0582 was given i.p. in doses of 1 mg/g bodyweight or 0·25 mg/g 20–30 minutes before the start of irradiation. Metronidazole was given i.p. in a dose of 0·25 mg/g 20–30 minutes before the start of irradiation. ICRF 159 was given i.p. at a dose of 30 μg/g daily from the time of tumour cell injection until irradiation.

RESULTS

Cellular radiosensitivity of hypoxic cells of WHT Aq. Ca. "G"

Figure 2 is a plot of $\log_{10}$ TD_{50} values (±2 S.E.) versus radiation dose for cell suspensions obtained

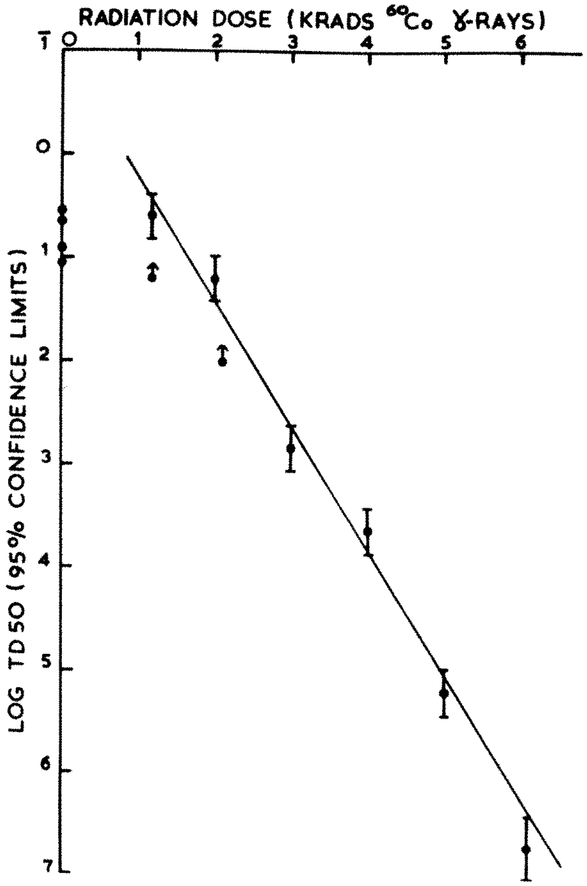

FIG. 2.

Plot of $\log_{10}$ TD_{50} for subcutaneous transplantation assays of WHT Sq. Ca. "G" cell suspensions prepared from tumours exposed to various doses of irradiation *in situ*, in killed (anoxic) mice. The slope of the weighted regression line indicates a D_0 of 352±20 rad. Points plotted at zero radiation dose are control assays. Confidence limits for these, omitted for clarity, are of the same order of magnitude as for the irradiation assays.

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[*] Many factors may act to flatten the tumour control probability curve from its theoretical slope. These will be considered in detail elsewhere.

from tumours which had been irradiated *in situ* in killed (anoxic) mice. The curve was fitted by weighted least squares linear regression and indicates a D_0 value of 352±20 rad ^{60}Co γ rays (95 per cent confidence limits), with an intercept at zero dose of $-1{\cdot}05$ logs. Applying an RBE correction of 0·85 gives a D_0 of ~300 rad for 250 kV X rays as used in TCD_{50} experiments. Control values of $\log_{10}$ TD_{50} for unirradiated tumour cells in three assays were in the range 0·58–0·92. A period of anoxia equal to the greatest duration of irradiation was shown not to alter significantly this control value (1·06). From these data, the extrapolation number of the survival curve for these cells is in the range 43–93 (best estimate from pooled control data ~60). This is an unusually high value compared with most other mammalian cell systems (Elkind and Whitmore, 1967), though not unique, *e.g.* Barranco *et al.* (1971) described three lines of human malignant melanoma cells with radiation survival curves having extrapolation numbers of ~40.

TCD_{50} assays in clamped and unclamped superficial cutaneous tumours (5–6 mm diameter × 1–2 mm thick)

In air-breathing mice, TCD_{50} values for unclamped tumours were, in three separate assays 3,324±105, 4,257±119 and 3,986±122 rad. For clamped tumours of the same size, the TCD_{50} values were 5,292±120 rad and 5,201±140 rad. With a knowledge of the hypoxic cell-survival curve parameters and the TCD_{50} for clamped tumours, the mean number of clonogenic cells per tumour can readily be calculated[*] as $\sim 5{\cdot}3 \times 10^5$. A TCD_{50} of 3,324 rad would be consistent with only $\sim 10^3$ hypoxic clonogenic cells, so that the hypoxic fraction in these unclamped tumours must have been <1 per cent. The highest unclamped TCD_{50} value obtained (4,257 rad) corresponds to a hypoxic fraction of about 3 per cent. The reason for this variability is uncertain, but we speculate that it may be due to slight differences in the depth of invasion of the "superficial" tumours. It does not appear to be an artifactual difference due to inclusion of more "provisionally cured" mice in any assay (Table I). Further consideration of this matter is in the Discussion.

TCD_{50} assays for tumours implanted or invading subcutaneously

Tumours implanted intradermally, but allowed to grow to a size of 7–9 mm diameter × 3–4 mm thick, with deep invasion of subcutaneous tissues, had a TCD_{50} of $\geqslant$ 5,544 rad unclamped. The designation of a minimum for TCD_{50} is due to the fact that all but one of the mice in this experiment died prematurely of metastases. Although these tumours were some five times larger than "superficial" tumours, such a volume difference would increase the TCD_{50} by only 483 rad *provided* the hypoxic fraction remained unaltered. It can, therefore, be deduced that the hypoxic proportion of cells in these tumours is greater than in superficial lesions, and is estimated at $\geqslant$46 per cent.

Tumours implanted subcutaneously and irradiated unclamped when they reached a mean diameter of 6–7 mm (*i.e.* of similar volume as the invasive cutaneous tumours), had minimum TCD_{50} values of 5,795±148 and $\geqslant$5,520 rad. Thus, one may infer that the hypoxic fraction of cells in these tumours is also much greater than in the superficial lesions.

Effect of Ro–07–0582 on TCD_{50} of unclamped superficial tumours

This drug is a preferential radiosensitizer of hypoxic cells (Adams, 1973). When given at a dose of 1 mg/g body weight, the drug reduced the TCD_{50} to 1,862±120 rad. Depending on which control value is taken for the TCD_{50} in mice which received no drug, the "enhancement ratio" is 1·79–2·29.

From the radiation survival parameters for hypoxic cells, 1,862 rad would kill very few hypoxic cells, indicating that in this experiment the drug had effectively eliminated the hypoxic element and tumour cure was probably governed by cells in the "oxic" or "sensitized" compartments.

It is perhaps significant that the TCD_{50} value for cutaneous tumours in which the hypoxic element has been eliminated is of the same order as the single dose cure level for human skin cancers (see Discussion).

Ro–07–0582, at a dose of 0·25 mg/g, effected a reduction of TCD_{50} from 3,986±122 rad to

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[*] The calculation is as follows: the probability of cure (P_{cure}) is the probability that there will be zero surviving clonogenic cells in the tumour. From Poisson statistics

$P_{\text{cure}} = e^{-m}$ where m = mean number of surviving cells

Now $m = \text{S.F.} \times \text{N}$ where S.F. = the surviving fraction of cells after irradiation and N = the total number of clonogenic cells in the tumour.

i.e. $P_{\text{cure}} = e^{-\text{S.F.} \times \text{N}}$.

At the TCD_{50}, $P_{\text{cure}} = 0{\cdot}5$.

$$\therefore \ln 0{\cdot}5 = -\text{S.F.} \times \text{N} \text{ or } \text{N} = \frac{\ln 2}{\text{S.F.}}$$

To calculate S.F., use of the approximation $\text{S.F.} = ne^{-D/D_0}$ is sufficiently accurate at the relatively high radiation doses being considered.

TABLE I

Outline of WHT Sq. Ca. "g" TCD_{50} Experiments

Tumour size/site	Clamped/unclamped	Drug	$TCD_{50} \pm SE$	Provisional cures / Total cures
5–6 mm dia. × 1–2 mm thick superficial intradermal	unclamped	—	3,324 ± 105	6/14
		—	4,257 ± 119	6/14
		—	3,986 ± 122	6/20
5–6 mm dia. × 1–2 mm thick superficial intradermal	clamped	—	5,292 ± 120	2/15
		—	5,201 ± 140	3/15
5–6 mm dia. × 1–2 mm thick superficial intradermal	unclamped	Ro-07-0582 1 mg/g	1,862 ± 120	3/30
		Metronidazole 0·25 mg/g	3,337 ± 123	6/23
		Ro-07-0582 0·25 mg/g	2,134 ± 245	8/32
7–9 mm dia. × 3–4 mm thick invading subcutaneously	unclamped	—	⩾5,544	11/12
		ICRF-159 30 mg/kg/day	4,642 ± 134	3/16
	clamped	ICRF-159 30 mg/kg/day	5,337 ± 150	2/17
6–7 mm dia. implanted subcutaneously	unclamped	—	5,795 ± 148	4/9
		—	⩾5,520	9/11

2,134 ± 245 rad. Both these assays were done concurrently on the same batch of tumours so that no ambiguity as to the correct control value arises. The "enhancement ratio" here is 1·87.

Effect of metronidazole

At a dose of 0·25 mg/g, this drug, which is also a preferential sensitizer of hypoxic cells (Foster and Willson, 1973), reduced the TCD_{50} of superficial cutaneous tumours from 4,257 ± 110 to 3,337 ± 123 rad in concurrent assays, yielding an "enhancement ratio" of 1·28. This compares with 1·87 for the same dose of Ro-07-0582.

Effect of ICRF 159

This drug has been reported by Salsbury *et al.* (1970) to "normalize" tumour vasculature, and it was hypothesized that by pre-treatment of mice with the drug from the time of cell injection up to the time of irradiation, the vascularization (and hence oxygenation) of the tumours might be improved. The drug is also an efficient inhibitor of metastases in this system (Peters, 1975) and this permitted the use of larger invasive tumours for TCD_{50} assays without an excessive loss of mice from metastases. For unclamped invasive tumours of 7–9 mm diameter × 3–4 mm thick the TCD_{50} in ICRF 159 treated mice was 4,642 ± 134 rad compared with ⩾5,544 rad for untreated controls. For clamped tumours in ICRF 159 treated mice, the TCD_{50} was 5,337 ± 150 rad. Thus, one can deduce that the drug has some radiosensitizing property, but the fact that the TCD_{50} for clamped tumours in ICRF 159 treated mice was lower than that for unclamped tumours in control mice suggests that the effect of ICRF 159 cannot be explained entirely in terms of improved tumour oxygenation.

Discussion

The tumour used in these experiments produced distant metastases, resulting in a variable loss of mice from experiment to experiment. As most (75 per cent) local recurrences were evident within 30 days,* we have included in our analysis mice which died with primary sites clear more than 30 days after treatment as "provisional cures". The bias produced by including mice in the "provisional cure" category would be to underestimate the TCD_{50} if any of these animals should subsequently have developed a local recurrence, had they lived 100 days. The conventional approach of excluding such animals would have left too few mice per group for useful TCD_{50} estimates in many assays, and, furthermore, to exclude them would still have biased the results unless one could show that the proportion of subclinically recurrent lesions in the animals dying prematurely was the same as the proportion of macroscopic recurrences in the remainder of each dose group.

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*The measured doubling time for small implants of this tumour was ⩽one day, and 30 notional doubling times should allow most recurrences to manifest themselves. Later recurrences probably reflect a slowing of tumour growth rate due to a "tumour-bed effect" of irradiation.

The quoting of exact numbers for TCD_{50} is not meant to imply single rad precision in their derivation (which is clearly impossible). The numbers are quoted simply for comparative purposes, with the knowledge that the absolute TCD_{50} values would be different. An examination of provisional cures for each assay in the table permits the following observations:

(1) The TCD_{50} values for unclamped "invasive" tumour of 7–9 mm diameter × 3–4 mm thick and for clamped subcutaneously-implanted tumours 6–7 mm diameter are certainly underestimates, as practically all of the "cures" in these assays were provisional.

(2) Few premature deaths occurred in assays using the drug ICRF 159 which is a potent inhibitor of metastases in this system. Thus, the TCD_{50} values for these assays are close to absolute values and indicate a definite reduction of TCD_{50} compared with the control assays.

(3) The assay of unclamped subcutaneously implanted tumours included a high proportion of provisional cures and the TCD_{50} value is probably low.

(4) The variability in TCD_{50} for unclamped superficial tumours 5–6 mm diameter × 1–2 mm thick cannot be explained on the basis of the proportion of provisional cures in each assay.

(5) For superficial tumours, the TCD_{50} in mice treated with Ro–07–0582 at 1 mg/g is close to absolute, since few provisional cures were included. As all three control assays included more provisional cures, the enhancement ratios derived from Ro–07–0582 at 1 mg/g are *lower* estimates.

(6) For other assays, approximately equal proportions of provisional cures were included, so that comparisons are legitimate, even though the absolute TCD_{50} values are possibly higher.

The series of experiments indicates that the proportion of hypoxic cells in this tumour system varied considerably with the site and/or size of the tumour transplants, from <1–3 per cent for superficial tumours of 5–6 mm diameter × 1–2 mm to $\geqslant 46$ per cent for invasive tumours of 7–9 mm diameter × 3–4 mm. Suit and Maeda (1967) reported a change in the hypoxic fraction of their C_3H mammary tumour from 0·2 per cent to 20–25 per cent when lesions of 0·6 mm^3 and ~ 250 mm^3 were compared. The size difference in Suit's tumours is much greater than the five-fold difference in our experiments, and we consider that the site of tumour growth was of more critical importance than tumour size in determining the hypoxic fraction, especially as three TCD_{50} assays of tumours implanted intradermally and irradiated at the same nominal size varied by up to 1,000 rad. A critical assessment of the accuracy of tumour volume measurement in the range of sizes used by us lead us to believe that the maximum discrepancy in tumours of the same nominal size would be very unlikely to exceed a factor of three, and this range of tumour size could not account for the differences in TCD_{50} values observed. Histological sections taken randomly from different batches of cutaneous tumours showed no gross differences in the relative proportion of viable and necrotic areas such as might cause a variability in clonogenic cell number for the same sized tumours. Another possible source of variability in TCD_{50} assays—immunological incompatibility between tumour and host—was excluded in formal tests reported elsewhere (Peters, 1975). One might speculate that the variable TCD_{50} values obtained for cutaneous tumours were due to small differences in the thickness (*i.e.* depth of invasion) of the superficial tumours, reflected in a variable hypoxic cell fraction. Even with the highest TCD_{50} for superficial tumours, however, the calculated hypoxic fraction was small compared with that for deeply invasive tumours. Such a finding may help to explain the clinical observation of increased "radioresistance" in deeply infiltrative tumours of, for example, the uterine cervix.

Although the superficial tumours had a relatively low proportion of hypoxic cells, calculations show that unless the well oxygenated cells had a D_0 as high as 192 rad, which is most unlikely, the hypoxic cells determined the cure probability for the tumours. Direct evidence of the truth of the deduction was provided by the effect of the specific sensitizer of hypoxic cells, Ro–07–0582, in reducing the TCD_{50} for superficial tumours to 1,862 rad. Doses of this order would kill very few hypoxic cells (based on our measured parameters) and it is a reasonable assumption that with this drug cure probability was determined by the oxic or sensitized cells. If the former assumption is true, we may deduce an OER for the tumour of $5{,}292/1{,}862 = 2{\cdot}84$, a value comparable with most other estimates of the oxygen ratio for mammalian cells (Elkind and Whitmore, 1967). The TCD_{50} for "oxic" tumours, 1,862 rad, is of the same order as that for human skin carcinomata (Widmann, 1941), which could be construed as suggesting that the human lesions contain no hypoxic cells. However, without other evidence, we cannot exclude the alternative possibilities enumerated in the introduction.

The efficiency with which Ro–07–0582 reduced the TCD_{50} in the system is noteworthy, especially at the lower doses of 0·25 mg/g bodyweight, where an enhancement ratio of 1·87 was observed. This value is high compared with reported enhancement ratios in some other murine test systems, *e.g.* Hewitt and Blake (1974) observed no detectable change in the surviving fraction of a murine squamous carcinoma exposed to 1,000 or 1,800 rad after two injections of 0·436 mg/g of Ro–07–0582, while other investigators have observed enhancement ratios of 1·2–1·7 (see Fowler and Adams, 1975). One possible explanation for Hewitt's negative finding is that he was using a much higher level of cell survival than obtains in TCD_{50} experiments; but the radiation doses he used were still considerably greater than the incremental doses used in clinical fractionated radiotherapy, and caution should be exercised in extrapolating experimental data using large single doses to the prediction of possible therapeutic benefits.

Metronidazole at a dose of 0·25 mg/g produced, in this system, an enhancement ratio of 1·28 which, though significant, is considerably lower than that achieved by Ro–07–0582 at the same dose (1·87). This marked superiority of Ro–07–0582 at low doses contrasts with results obtained in artificially hypoxic skin by Denekamp *et al.* (1974) who found that the relative advantage of Ro–07–0582 at high doses largely disappeared at 0·25 mg/g because of a flatter dose response curve for metronidazole. Stone and Withers (1974) found that a dose of metronidazole of ~0·1 mg/g produced equal enhancements of 1·2 in the responses of a C_3H mammary tumour and of normal skin reactions, so that no "therapeutic gain" was achieved. The jejunal epithelium, however, was not sensitized by metronidazole – in fact a protective effect was observed at high radiation doses. Enhanced responses of both neoplastic and artificially hypoxic normal tissues have been observed in preliminary clinical trials of Ro–07–0582 (Adams *et al.*, 1976) but it is too early to tell whether any useful therapeutic gain is possible with agents of this type.

The effect of ICRF 159 in producing a modest reduction of TCD_{50} in this tumour system deserves comment. The hypothesis was tested that by modifying the tumour vascularity, this drug might improve oxygenation. However, the reduction in TCD_{50} observed in both clamped and unclamped tumours suggests that this is probably not its only effect. Moreover, the extent of vascular "normalization" observed in this tumour (Peters, 1975) was much less striking than that seen in the Lewis lung tumour (Salsbury *et al.*, 1970). The mechanism by which ICRF 159 reduced the TCD_{50} of our tumours is uncertain. It could be that partial redistribution of tumour cells into G2 (Hallowes *et al.*, 1974) resulted in some radiosensitization, but a simple adjuvant chemotherapeutic effect cannot be excluded.

In an uncontrolled preliminary clinical trial of ICRF 159 as a "radiosensitizer", Ryall *et al.* (1974) observed unexpectedly favourable responses in a variety of sarcomas. Early skin reactions were exacerbated by the drug, but lung tolerance appeared unchanged, at least in the short term.

ACKNOWLEDGMENTS

Thanks are expressed to Dr. H. B. Hewitt who provided the mice and tumour used in these experiments and to Misses E. Blake, S. Ayres and A. Walder who assisted with various experiments. The TCD_{50} computer program was produced in collaboration with Dr. E. H. Porter to whom credit for the development of the program is due. The cost of the research was met by the Cancer Research Campaign.

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Book reviews

Biomedical Dosimetry. Proceedings of a Symposium, Vienna, 10–14 March 1975, pp.709. (Austria, International Atomic Energy Agency), £18·70.

This volume appeared in the late autumn of 1975, commendably soon after the conference was held. Only direct photographic reproduction of copy supplied by the authors can make such rapidity possible.

The conference covered eight main areas, namely neutron dosimetry, thermal neutron capture therapy, new dosimetric techniques, physical aspects of radiotherapy with photons and electrons, standardization, diagnostic radiology, dosimetry of megavoltage photons and electrons, and ingested radionuclides. There is a total of 49 papers, plus discussion.

The general standard of the papers is high, and it is invidious to pick out individual ones for comment. Nevertheless, some remarks are called for even if these reflect only my personal interests. The opening paper by Bichsel *et al.* discusses the principles of dosimetry of mixed neutron plus γ radiation and suggests that proportional counters may be able to separate the field into two qualities better than measurements to distinguish between neutrons and photons. Burger *et al.* discuss the uncertainties in the twin chamber technique and assess the likely change in RBE in the penumbra. Frank *et al.* describe new Si diodes which may be a useful method of clinical dosimetry. Production and properties of a neutron beam from a D$_2$ gas target using a relatively small cyclotron is described by Lorenz *et al.*

The section on thermal neutron capture therapy is of particular interest as this method of treating gliomas has been revived in Japan with encouraging results. Murray *et al.*, at MIT suggest that neutrons from ^{252}Cf moderated by D$_2$0 and filtered by ^{10}B would provide a beam superior to any studied heretofore for treatment of bone tumours in addition to tumours in the brain.

A new method of computerized treatment planning is described by Böhm *et al.* which is based on transport theory for the radiation beam rather than empirical fits to measured data. This method is particularly suitable when allowance is to made for tissue inhomogeneities. Direct use of ultrasonic scans in treatment planning is described by Slater *et al.* Boag reviews xeroradiography and ionography, while Haus *et al.* discuss improvements in quality of conventional radiographs without increasing the dose received by the patient. In the section on high-energy dosimetry a particularly important paper is the one by Berger *et al.* who present new calculations of stopping-power ratios for electrons from 1 to 60 MeV and at depths in the phantom up to 32 cm. The authors also made measurements with a carbon calorimeter and ionization chamber with which they have been able to verify the calculations experimentally. Wambersie *et al.* have used the Fricke dosimeter to obtain experimental values of correction factors C$_E$ for ionization chambers exposed to electrons, and to measure ionization loss by recombination.

There are many other papers of a high standard and the book will be a useful source of information for many years.

D. K. Bewley.

Applied Surgical Pathology. Edited by Angus E. Stuart, Adam N. Smith and Eric Samuel, pp. 1112, 1975. (Oxford, London, Edinburgh, and Melbourne, Blackwell Scientific Publications), £38·00.

This book, about 1,100 pages in length, is a tri-partite production which should prove valuable to surgeons and radiologists both in clinical practice and in preparing for Fellowship examinations. The clinical orientation of the text is clearly evident throughout the book, and unlike many standard pathology works the presentation is such that reading is a pleasure rather than a chore. All the basic pathology is fully discussed in the early chapters – extensive coverage in this section is also given to immunology and malignant disease. The following 16 chapters are devoted to the different organs and tissues—all the chapters are written by experts in their fields. The illustrations throughout the book are clear and well chosen and the book is not bedevilled by profuse reproductions of microscopic sections which tend to lessen the readability of so many pathological texts. The references are up to date and show a wide eclecticism. Altogether a most valuable and useful book and a pleasure to review.

J. A. Gleeson.

1976, *British Journal of Radiology*, 49, 716–718

Technical notes

An after loading colpostat (using standard source tubes)

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ABSTRACT

An afterloading system for the treatment of gynaecological patients is described. It uses a rigid tandem to which afterloading colpostats are attached. The catheters for afterloading the colpostats are flexible thus minimizing patient discomfort. A constant 90 deg. alignment of source tubes between the uterine tandem and colpostats is achieved.

Several afterloading systems such as the Fletcher-Suit (1963) and Scott (1973) systems are available for the treatment of gynaecological neoplasms. Most of them are modifications of the Paris or Manchester tandems and colpostats. The present paper describes a variant of afterloading colpostats which permits the easy introduction, removal or change of radioactive sources (radium or caesium tubes) in patients away from the operating room and after packing of the vagina.

The main advantages of these afterloading colpostats are:

(1) easy introduction of the colpostats through the vulva with assembly of the separate portions of the system in the upper vagina against the cervix;

(2) minimal patient discomfort during the time of the application since only small and flexible tubes extrude through the vulva;

(3) a constant 90 deg. alignment of source tubes between tandems and colpostats.

DESCRIPTION

The colpostat system consists of three portions assembled by two dove-tail joints.

1. The central portion B, Fig. 1, consists of a piece of plastic material with:

(a) two tenons, one in each of its transverse ends (a tenon is a projecting wedge-shaped part that fits into a corresponding indentation called a mortise; the joint thus formed is called a dove-tail joint);

(b) a central orifice through which a rigid tandem (A, Fig. 1) is inserted;

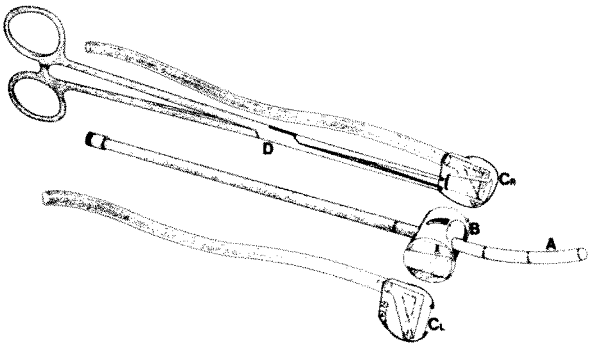

FIG. 1.

Schematic view of the afterloading system.
The rigid tandem A is inserted through the centre of Piece B, which is secured to the tandem by means of a small screw. Piece B comes in different transverse diameters. The afterloading colpostats, C_R and C_L, are joined by a dove-tail joint to the central piece after insertion into the upper vagina by means of Forceps D.

(c) a smaller hole in its anterior portion for suturing this central piece to the cervix, if necessary;

(d) a stainless steel screw located in its posterior surface. When tightened it fixes the central piece to the metal tandem thus immobilizing the system. We have made several different transverse sizes for the central piece. The one to be used will depend upon the width of the patient's vagina.

2. Two colpostats, one for the right and the other for the left side of the upper vagina, C_R, C_L, Fig. 1. The medial surface of the colpostats has a mortise that fits the tenon of the central piece, described above. The proximal and lateral surfaces of the colpostats have the same shape and configuration as a 2·5 cm Manchester ovoid. The distal part of the colpostat has a long flexible tube in its anterior portion designed for the introduction of the radioactive source after packing of the vagina. The outside diameter of this tube is 0·95 cm. The distal surface of each colpostat has two holes that allow the insertion of the ends of straight forceps. When clamped,

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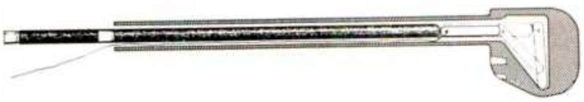


FIG. 2.

Schematic view showing the insertion of a source tube into the afterloading colpostat.

The source, attached to a long string is pushed with a rod through the lumen of the flexible tube into the central portion of the colpostat, where it falls to a vertical position. It is maintained vertically by pushing the rod against the upper end of the source tube. The rod is taped to the distal end of the colpostat tube to forestall its coming out.

the forceps will hold the colpostats rigidly thus permitting introduction and manipulation of the colpostats in the vagina.

At the centre of each colpostat there is a cavity of triangular shape (Fig. 2). It has no connection with the outside surface of the colpostat, so that no aseptic procedures are necessary in the simulator rooms or when loading the sources in the patient. The patient is supine during the loading of the colpostats. The radioactive tube will fall into this cavity in a vertical position after its introduction horizontally through the flexible tube.

The colpostats are of standard size and have an axis of 2·85 cm and a diameter of 2·50 cm so that they accommodate standard source tubes.

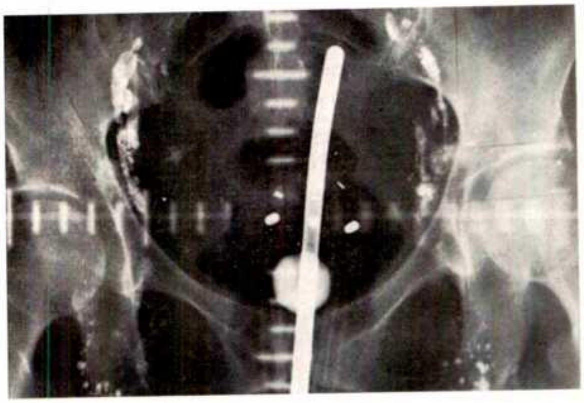
Procedure used for insertion of the colpostats

1. After the uterus is sounded and the width of the vagina determined, we insert a rigid afterloading tandem through the central orifice of Piece B (Fig. 1). The distance from the proximal end of Piece B to the end of the tandem is equivalent to the size of the uterine cavity. If desired, Piece B can be sutured to the cervix, although with appropriate packing this step is not necessary. The screw at the posterior surface of Piece B is tightened thus securing this piece to the tandem. The tandem is inserted into the uterus.

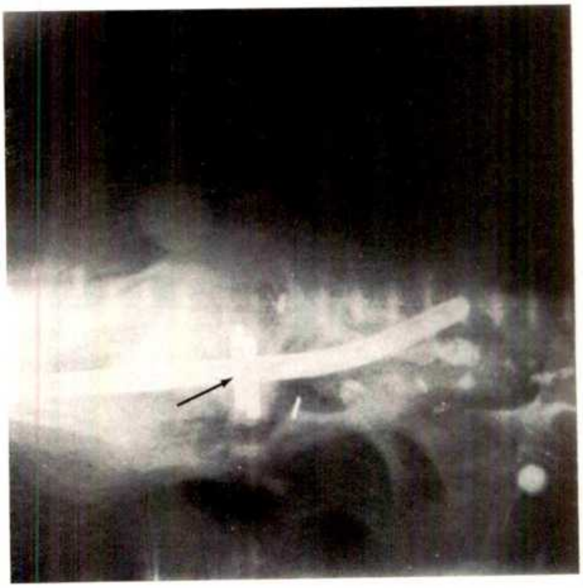
2. Each colpostat (C_R, C_L, Fig. 1) is then introduced into the vagina one at a time and interlocked with the central piece. Long straight forceps are clamped to the holes of the distal part of the colpostats and secured firmly. This allows easy manipulation in the upper vagina. When tenon and mortise are aligned, the colpostat is pushed slowly to its maximum travel.

3. Vaginal packing is done in the usual fashion.

4. Dummy sources (non-radioactive) are introduced into the tandem and colpostats to display their position on radiographs and thus help in planning



(A) Antero-posterior view of the system.



(B) Lateral view of the system.

FIG. 3.

Radiographs of the system applied to a patient

Films show dummy tubes in colpostats and tandem, to check for positioning.

Notice the 90 deg. alignment between sources in tandem and colpostats. Also the centre of the colpostat sources is always at the level of the rigid tandem (see arrow). With this system it is not possible to place the colpostats in the anterior or posterior fornices. Metal clips indicate the position of the cervix.

the number of sources, their strengths and subsequent location for afterloading.

To load the system with radium or caesium tubes, we follow the following procedure:

1. To load the colpostats:

(a) With the patient supine, the dummy tubes in the colpostats are removed by pulling them with a

1976, *British Journal of Radiology*, *49*, 718–722

string previously tied to their anterior end. The tandem sources are removed by withdrawing the plastic tube in which they were initially inserted.

(b) A long thin string (silk, nylon, etc.) is attached to one end of the radium or caesium tube. The tube is pushed forward with a flexible rod through the catheter attached to the colpostat as shown in Fig. 2. The source tube in the colpostat is maintained in a vertical position by pushing the flexible rod against the tube and taping it to the end of the colpostat catheter.

2. The metallic afterload tandem is loaded in the conventional fashion. Verification radiographs are obtained which may be used also for dose calculations.

To remove the system, the sources are pulled out first and placed in appropriate containers. In this way, the rest of the procedure is done without further exposure to the operator. The packing is removed and colpostats and tandems are withdrawn. This procedure is done with minimal discomfort to the patient.

We have found this system to be flexible since it adapts itself to any width of the upper vagina. It is also easy to introduce and load with radioactive sources without aseptic techniques. The alignment of sources between tandem and ovoids is a constant 90 deg.

ACKNOWLEDGMENT

The authors wish to acknowledge the help of Mr. Harry Gillen of the Department of Physics, University of Michigan, for tooling the colpostats described here.

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Gamma-camera uniformity as a function of energy and count-rate

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(*Received November, 1975 and in revised form March, 1976*)

Recently there has been some discussion on the dependence of the uniformity of a gamma-camera on the energy of the incident photons and on their count-rate (Hannan and Bessent, 1974; Jansson and Parker, 1975). Since in these cases only the results of a few investigations were reported it was considered worthwhile to examine this problem more thoroughly. This paper reports the results of experiments performed with a Picker Dynacamera 2C system.

SYSTEM DESCRIPTION AND EXPERIMENTAL SET-UP

The Picker Dynacamera is coupled to a PDP-8E computer through the image enhancement system (interface to the computer developed by Picker). The PDP-8E computer has a memory of 16K making possible pictures with 100 × 100 elements. An extended arithmetic element performs fast multiply/divide manipulations which are important for fast corrections of non-uniformity. The data are stored on a 1·6 million word disc (RK/8E from Digital Equipment). A Tektronix 4010 display terminal is used for programming and graphics purposes. A teletype is used for producing hard copies.

Black and white or coloured pictures can be made from an oscilloscope, using a computer driven "colour wheel" containing three filters (blue, green and red) and an opening for black and white pictures. Programs are available for all the functions necessary for processing nuclear medicine studies. A full account of the system has been published elsewhere (Hasman and Groothedde, 1973; 1975). All static studies are corrected for the non-uniformity of the crystal. The flood-field data are normally obtained in the following way.

The data are accumulated until about 3,500 counts are obtained (the maximum number of counts possible is 4,095). Four such collections are added so that the spread in the data is about 2 per cent. For the present study a cylindrical vessel was filled with water (depth about 20 cm) and thoroughly mixed with 30 mCi of ^{99}Tc^{m}. The data collection was started for a preset time. The results were then written onto disc. The same procedure was repeated every two hours. In this way 13 flood fields were

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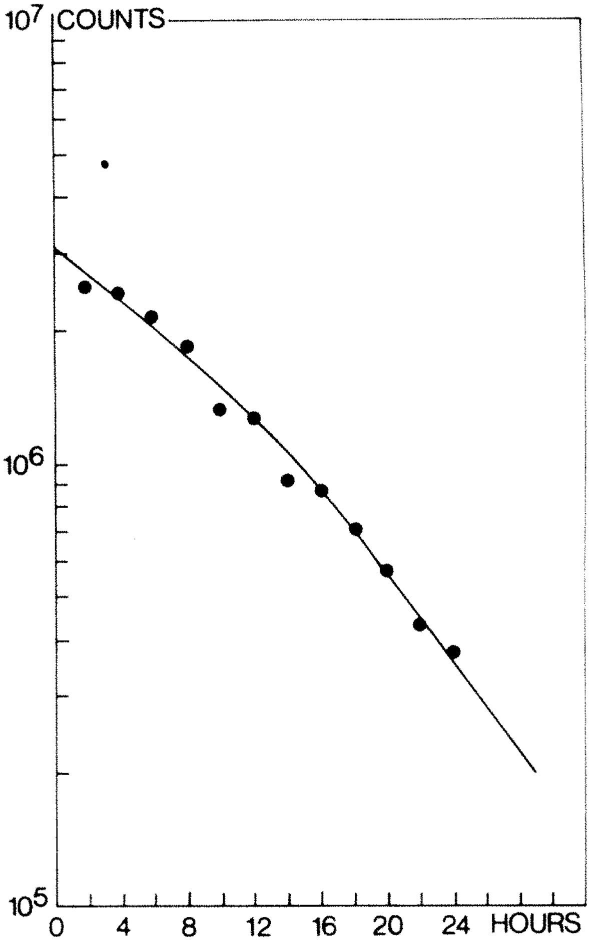

Fig. 1.

The total number of counts over the flood field shown as a function of time.

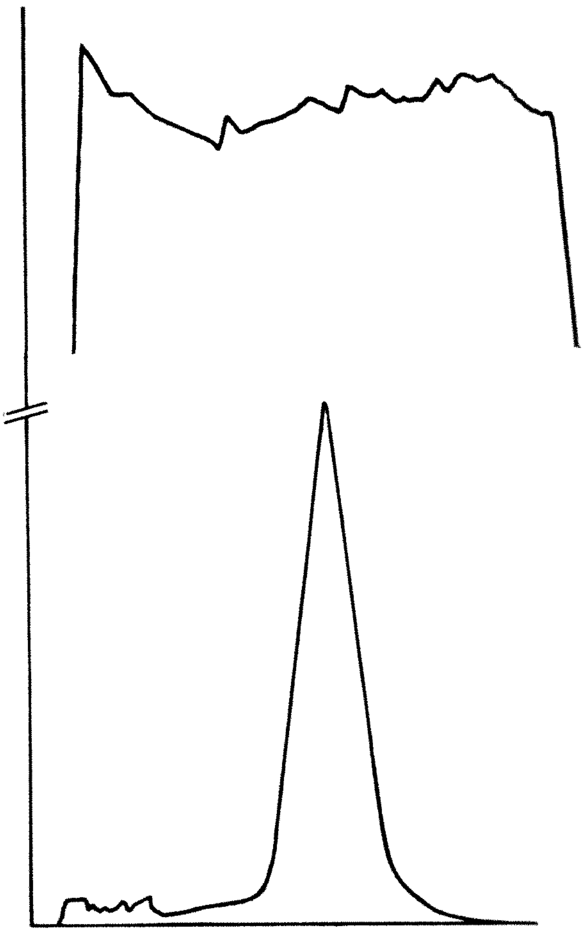

Fig. 2.

Comparison of the activity distribution through a slice (upper part) with the amplitude distribution representing the data over the whole picture (lower part).

obtained over a period during which the activity of technetium had been reduced by a factor of 16. In Fig. 1 the total number of counts over the flood field as a function of time is displayed. This gamma-camera has a dead time of 35 microseconds. Since a derandomizing buffer was built in, the actual dead time for low count-rates appears to be 17 microseconds. From Fig. 1 it can be seen that flood fields have been obtained with count-rates giving rise to relatively high dead times.

Results

The uniformity of the crystal is usually represented either by the original data as displayed on a Polaroid photograph or by a histogram representing the activity through a slice. The first method has the disadvantage that no figures on the overall uniformity of the crystal can be obtained. In the second method the results of the activity distributions through several slices have to be obtained. For "quality control" we adopted a third method. With this method, using a so-called amplitude histogram, it is possible to present all the relevant data on the uniformity in one histogram.

The amplitude histogram is constructed in the following way. The maximum number of counts in the picture is obtained first.The range from zero to this maximum is then divided into a hundred classes and each picture element is assigned to one of these classes according to the number of counts in that particular element. It follows that an ideal flood field consisting of elements containing an equal number of counts will give rise to a histogram having only information in the last class. The other classes are empty. In the actual situation the flood field is not

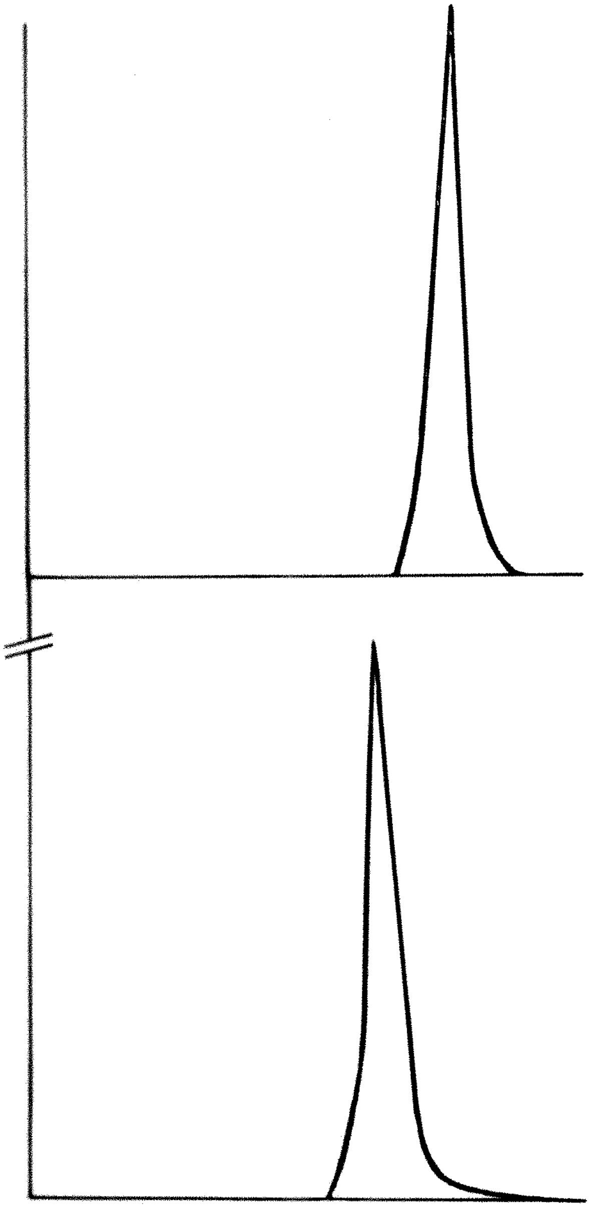

FIG. 3.

Amplitude distribution of the flood field obtained at the highest count-rate and corrected by the flood field obtained at the lowest count-rate (upper part). The lower part shows the amplitude distribution of a flood field obtained at medium count-rate corrected with the flood field obtained at the lowest count-rate.

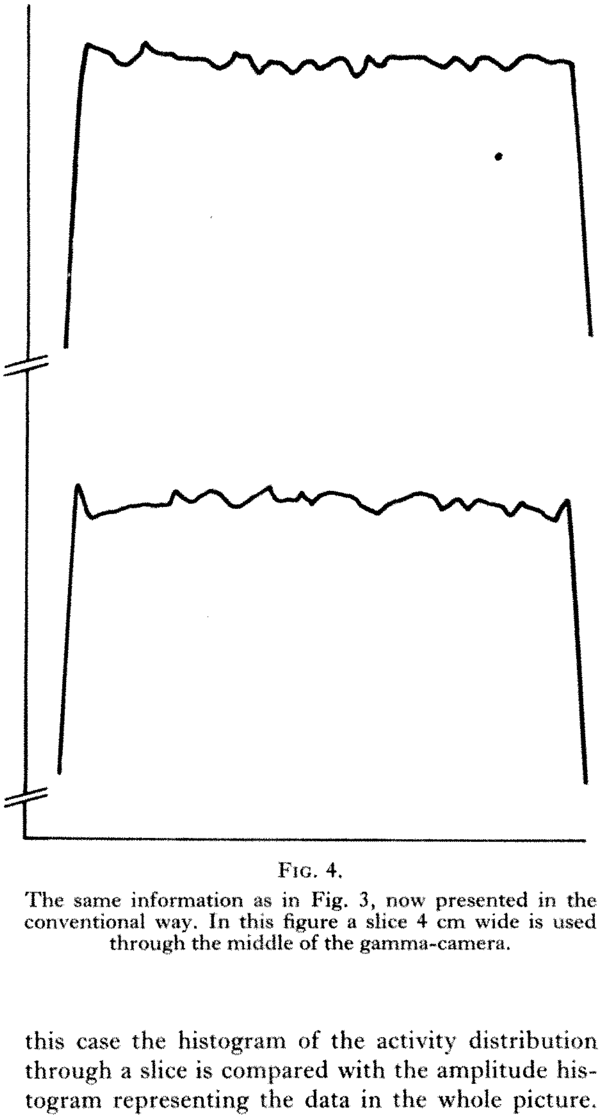

FIG. 4.

The same information as in Fig. 3, now presented in the conventional way. In this figure a slice 4 cm wide is used through the middle of the gamma-camera.

ideal and the resulting amplitude histogram displays a bell-shaped curve.

The broader the curve the worse the uniformity. In Fig. 2 a comparison is made between the method normally used and the method presented here. In this case the histogram of the activity distribution through a slice is compared with the amplitude histogram representing the data in the whole picture.

In the upper part of Fig. 3 the flood field obtained at the highest count-rate and corrected by the flood field obtained at the lowest count-rate is displayed. In the lower part of this figure the results are shown obtained with a flood field at medium count-rate corrected with the flood field at the lowest count-rate. Both curves are very sharp and similar, suggesting no dependence on the count-rate at all. The same information is displayed in Fig. 4 in the conventional way. Slices with a width of 4 cm were used here. From these pictures it is again clear that there is hardly any count-rate dependence.

The energy dependence of the uniformity was investigated in several ways. Using $^{99}\mathrm{Tc}^{\mathrm{m}}$ the uniformity distribution through a slice is displayed in Fig. 5 for three different energy settings. (The upper part of Fig. 5 gives the results for a symmetrical window; the middle part gives the results for a window comprising the lower half of the peak; and the lower part gives the results for the upper half of the peak). It is quite clear that the dependence on the window setting is appreciable.

In the second experiment a flood field obtained with ^{99}Tc^{m} was corrected by a flood field obtained with ^{57}Co. From Fig. 6 it is clear that the correction by ^{57}Co (using a symmetrical window around the cobalt peak) gives reasonable results (shown for two slices). Using the ^{99}Tc^{m} window for obtaining the ^{57}Co flood field gives worse results (lower part of Fig. 6).

The dependence of the uniformity on the type of collimator was also checked. As can be expected the uniformity is not influenced by the type of collimator used.

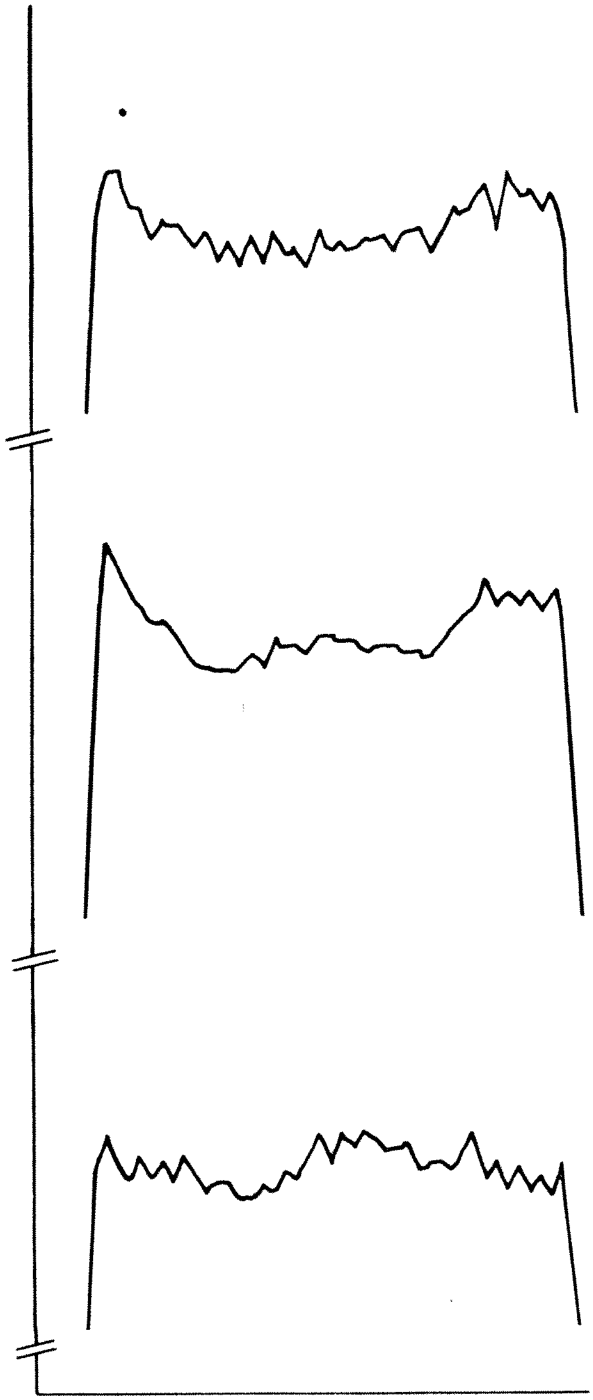

FIG. 5.

The flood-field distribution using three settings of the energy window. Upper part: symmetrical window; middle part: window comprising lower half of the peak; lower part: window comprising upper part of the peak.

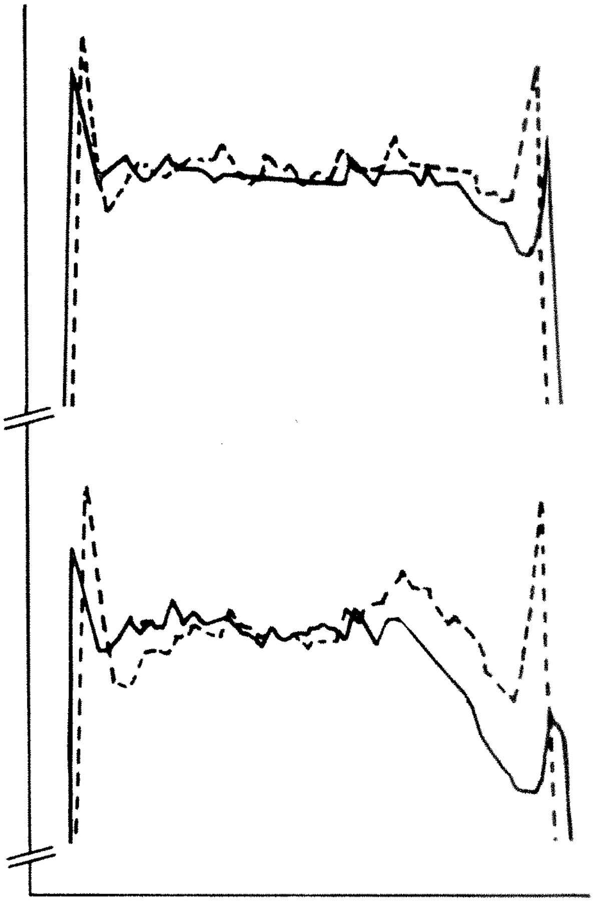

FIG. 6.

^{99}Tc^{m} flood field corrected by ^{57}Co (using a symmetrical window around the ^{57}Co peak) for two slices (upper part) and the ^{99}Tc^{m} flood field corrected by ^{57}Co (using a symmetrical window around the ^{99}Tc^{m} peak) for two slices.

CONCLUSIONS

The dependence of the gamma-camera uniformity was determined for several parameters. It could be concluded that the dependence on the count-rate is minimal. The uniformity is very sensitive to the window setting around the peak. If the window is centred symmetrically around the photo-peak the energy dependence is much less and different isotopes can then be used for checking the uniformity of the gamma-camera. Our results therefore, do not support the findings of Hannan and Bessent (1974) and are more in agreement with the findings of Jansson and Parker, although we do not see any dependence of the uniformity on count-rate. It should be stressed that different gamma-cameras were used in the papers cited (N.E.IV and PHO Gamma 3) whilst our data relate to the Picker Dynacamera 2C, so that no general conclusions can be drawn from the available data and every centre has to check the factors affecting uniformity on its own camera. The new method for presenting uniformity data which we describe here is convenient for this purpose.

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Book review

Primer of Medical Radiobiology. By Elizabeth L. Travis pp. xiv+241, illus., 1975 (Chicago, Year Book Medical Publishers, Inc.; London, Lloyd-Luke (Medical Books) Ltd.), £10·15.

The past few years have seen the publication of a relatively large number of text-books on radiation biology, most of them designed to meet the needs of a medical readership. It would seem that these might have saturated the interested market, but apparently not. This latest addition has been written for "radiologic technologists" and is aimed at students training to work as non-medically qualified technicians in the areas of diagnostic radiology, nuclear medicine and radiation therapy.

The subject matter is presented at an elementary level, is well written, adequately illustrated and provides a clear introduction to the field. Most of the main areas are covered, or at least mentioned, from cellular, tissue and whole body effects to the late manifestations of radiation injury. The last three chapters deal with the clinical uses of radiations. An extensive glossary completes the book.

In my view, the author has made out a good case for adding yet another volume to the medical radiobiological library by catering for the complete novice. However, such a basic treatment may lull the reader into thinking that this is the whole story. For example, although variations in the radiation sensitivity of cells as they progress through the cell cycle are described, it is not indicated that the details of these variations depend very much on the cell line being studied. Again, intracellular repair is dealt with only in terms of the sparing effect of dose fractionation with no mention of the molecular events which may be involved. The lists of references given at the end of each chapter should go some way to showing the student that the subject is far from simple.

In covering such a wide field, the author is to be congratulated for avoiding errors. The only important one I have come across is in the presentation of the relationship between relative radiation sensitivity of cells and oxygen tension in Fig. 10(4). She makes partial amends for this by showing the correct form of the curve in Fig. 4(10). However, I once heard of an unfortunate applicant who failed to obtain an appointment because of the same error.

I can certainly recommend this book to medical and non-medical students as a suitable introductory text, but the publishers might have tried harder to help this financially struggling group by setting a price nearer the range of its pockets.

N. E. GILLIES.

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Case reports

Abdominal pregnancy

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(*Received December, 1975*)

Abdominal pregnancy is rare. It usually occurs subsequent to rupture of a tubal pregnancy but may be secondary to a fertilized ovum implanted directly on a peritoneal surface. The incidence varies in different series ranging from approximately 1/3,000 deliveries to 1/15,000.

Abdominal pregnancy is one of the gravest complications to both fetus and mother. Ware (1948) and Beacham *et al.* (1962) noted a fetal loss of 75 per cent and 95 per cent respectively. Surviving infants may have an incidence of congenital malformations as high as 50 per cent. Maternal mortality has dropped from 50 per cent in 1889 to a modern day incidence of 2 per cent.

The clinical management of abdominal pregnancy, particularly the timing of operative intervention, remains a point of obstetrical debate. If the fetus is alive, waiting will increase the chance of fetal survival. Others would argue that the low survival rate of infants coupled with the high incidence of fetal abnormalities would not justify the potential hazards of maternal complications. When the fetus is dead, some might wait for placental regression, while others feel that the possible hazards of infection, haemorrhage, and perforation of the bowel would not justify further delay.

Although removal of the placenta is the most dangerous part of the operation, Hreschyshyn *et al.* (1961) noted that such removal lowered the complication rate from 72·4 per cent to 18·5 per cent, the readmission rate from 24 per cent to zero, and the rate of a second laparotomy from 40 per cent to 9·2 per cent.

As an aid to diagnosis, sonography may demonstrate the fetus or placenta outside the normal uterus and radionuclear imaging may indicate the site of the placenta. Pre-operative arteriography is of the utmost value, since removal of the placenta necessitates recognition and ligation of all avenues of blood supply.

CASE REPORT

N.Z., a 40-year-old white gravida five, para three was admitted because of vaginal bleeding and left-sided abdominal pain eight weeks after her last menstrual period. The uterus was thought to be at the upper limit of normal in size, irregular and tender. The urinary chorionic gonadotrophins were elevated on admission and again several days later. Bleeding subsided and the fetal heart was monitored on the day of discharge.

At subsequent visits and then at 17 weeks, the patient continued to complain of abdominal pain which became progressively severe. The doptone did not pick up a fetal heart but a loud souffle was noted over a position consistent with the left uterine artery in co-ordination with the patient's pulse. Abdominal palpation was difficult because of peritoneal irritation and abdominal guarding. At first, it was thought that the uterus extended as far as the umbilicus; however, a later examination suggested an intra-pelvic mass extending two fingerbreadths above the symphysis pubis. A pelvic examination indicated that the cervix was pushed up high behind the symphysis and there appeared to be large mass in the cul-de-sac. The uterus could not be identified.

An abdominal pregnancy, secondary to a ruptured tubal pregnancy was suspected and the patient was hospitalized.

A plain radiograph of the abdomen did not demonstrate any fetal parts. An abdominal aortogram was performed using a catheter introduced into the right femoral artery by the Seldinger technique. This showed marked hypertrophy of the left uterine artery and its tubal branch and slight enlargement of the right uterine artery. In the late arterial phase their branches outlined a slightly enlarged uterus in normal position. In the mid-arterial phase, there was filling of placental sinuses supplied extensively from the tubal branch of the left uterine artery and from a tortuous hypertrophied left ovarian artery. There was no identifiable supply from visceral or lumbar vessels (Figs. 1 and 2).

The placenta measured 10 × 7 cm in size and was located mainly over the left side of the true pelvis, lateral to the uterine artery. It drained by a markedly enlarged left ovarian vein (Fig. 3). The appearance suggested an abdominal pregnancy, presumably secondary to rupture of a left tubal pregnancy.

An exploratory laparotomy was performed after three days of blood transfusions. A slightly enlarged and completely empty uterus was identified. The right fallopian tube and ovary were oedematous but otherwise normal. A mass in the pouch of Douglas, which bled perfusely, was shown to be placental tissue. At the lowermost portion of this mass, an amniotic sac containing a fetus was identified. The placental tissue was partially removed but haemorrhage from the remaining portion which involved the left side of the pelvis and left uterine tube could not be controlled. A total hysterectomy, left salpingo-oophrectomy and removal of the residual placenta was performed. The extensive bleeding stopped when the left uterine artery was ligated. The patient was discharged on the tenth post-operative day, and has remained symptom free.

The pathologist noted that the uterus measured 9 × 5 × 4 cm. The cavity was only slightly enlarged and the endometrial lining was thickened to 4 mm and showed marked deciduoid change. The left fallopian tube and ovary showed evidence of attachment to the placenta which weighed 170 g. There was a well-formed male fetus measuring 12 cm in length and weighing 89 g (Fig. 4).

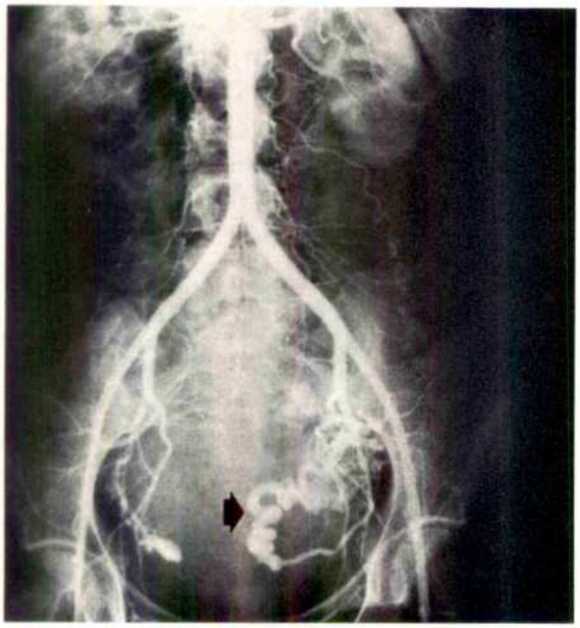

FIG. 1.
Early film of abdominal aortogram demonstrates marked hypertrophy of the left uterine artery (solid arrow).

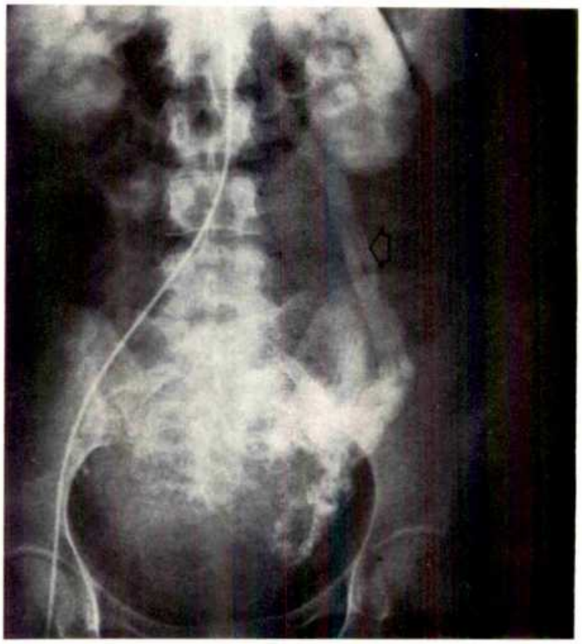

FIG. 3.
The venous drainage occurs mainly into what are most likely large left ovarian veins (open arrow).

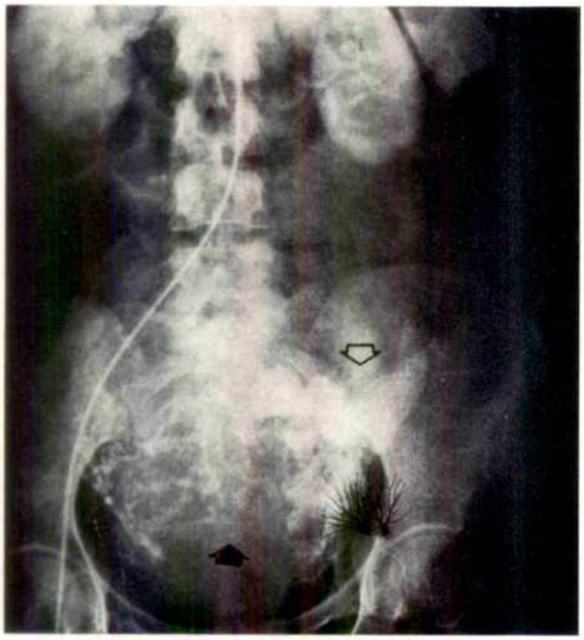

FIG. 2.
A later film demonstrates an area of sinusoidal filling on the left side of the pelvis (open arrow) outside of a relatively small uterus which is delineated by typical "corkscrew vessels" (solid arrow).

DISCUSSION

Many radiological signs of value in advanced abdominal pregnancy have been described. Cockshott and Lawson (1972) carefully reviewed all the radiological signs which may be of value in making the diagnosis of advanced abdominal pregnancy, and have grouped these appearances according to their degree of reliability. Table I has been modified from their paper. It is readily noted that the vast majority of the signs depend on the radiological visualization of the fetus. Cockshott concludes that hysterography as a diagnostic technique, is hazardous in the presence of a live fetus.

Radionuclide imaging has been advocated to determine the site of the placenta, but lacks the detailed morphological information that would be provided by angiography. It may be of more value on the sequential assessment of any retained placental fragments.

Sonography may be of value in the early diagnosis of extra-uterine pregnancy. Kobayashi (1974) finds the technique of value and clearly lays out the diagnostic procedures necessary for the diagnosis. Again, however, such a method of examination will not provide the evaluation of the blood supply so necessary for successful operative management.

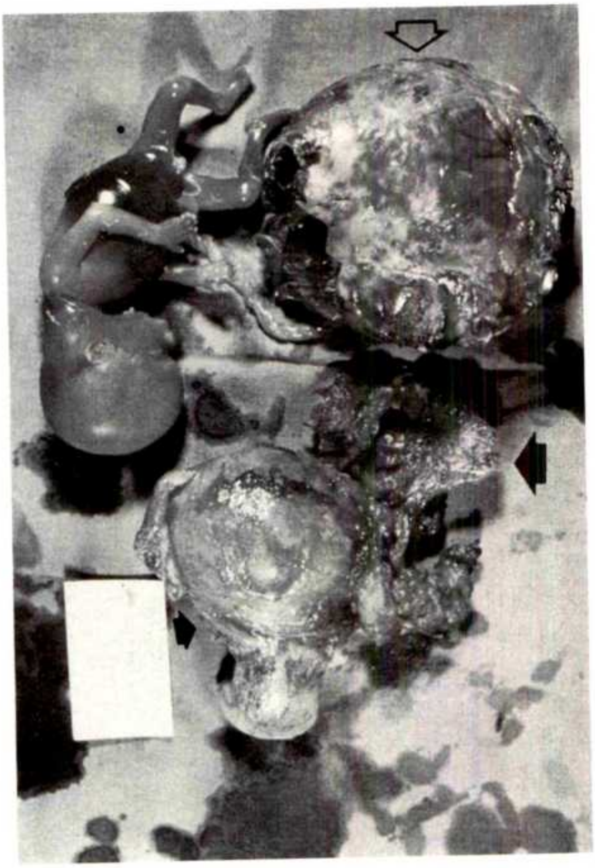

FIG. 4.

Complete surgical specimen demonstrating uterus (small solid arrow), remnant of left fallopian tube (large solid arrow), placenta (open arrow) and fetus.

TABLE I

RADIOGRAPHIC SIGNS OF ABDOMINAL PREGNANCY

- I. Non-invasive.
  - Conclusive:
    - *Lithopedion.
    - Intimate application of fetus to maternal abdominal wall.
  - Indicative:
    - Free gas outlining the abdominal gestational sac.
    - Hydramnios outlining the gestational sac above the pelvis.
  - Suggestive:
    - *High fetal position with a bizarre lie.
    - *Fetal overlap of the maternal spine in the lateral projection.
    - *Gas (other than rectal) below the presenting part.
  - Doubtful or misleading:
    - *Increased clarity of the fetal parts.
    - *Immobility of the fetus.
    - *Maternal intestinal gas overlap in two planes.
- II. Invasive techniques.
  - Conclusive:
    - Pelvic angiography.
    - Hysterography (contra-indicated if fetus is alive)
  - Doubtful or misleading:
    - Cystography.
  - Contra-indicated:
    - Pneumoperitoneum and pelvic pneumography.
    - Direct uterine myometrial venous studies.
    - Amniography.

*Necessitates visualization of fetal parts.

An understanding of the normal uterine and placental blood supply is essential. The arterial supply to the uterus is primarily from the uterine artery, a branch of the anterior division of the internal iliac artery. This artery runs medially along the levator ani in the broad ligament reaching the side of the uterus. It ascends between the layers of the broad ligament to the junction of the uterus and fallopian tubes. The artery then divides into fundal, tubal and ovarian branches. During normal pregnancy, the myometrial branches hypertrophy and the uterine arteries become more lateral in position as uterine enlargement proceeds. The ovarian arteries which arise from the abdominal aorta also hypertrophy during normal pregnancy and may participate in placental blood supply. The enlargement of the uterine and ovarian arteries is symmetrical. Placental sinuses are noted as mottle densities of varying size and shapes, with villi causing irregular filling defects. Placental sinuses may also be seen in tubal pregnancies but are rarely seen in abdominal pregnancy (Borrell *et al.*, 1953).

In abdominal pregnancy only the vessels supplying the placental site are enlarged. Hreschyshyn *et al.* (1961) have shown that in 17 per cent of the cases, the placenta received its blood supply from sources other than the genital tract. In 12 per cent of the cases, the placenta extended to or was confined solely to the abdomen. Consequently, it is necessary to include the upper abdomen and all the visceral and lumbar arteries to assure that the placenta and its supply will be visualized.

Cockshott and Lawson (1972) analysed the pelvic angiograms of eight patients with advanced abdominal pregnancy and found that at least one ovarian vessel was enlarged in all eight. Only one patient showed enlargement of a uterine vessel. The authors found this easy to explain on the basis that most abdominal pregnancies follow a ruptured tubal gestation. In the case that we report, there is marked enlargement of the tubal branch of the uterine artery and much less hypertrophy of the associated ovarian artery. The difference probably merely indicates that the initial site of nidation occurred more to the

1976, *British Journal of Radiology*, *49*, 726–728

uterine than the ovarian side of the arterial anastomosis in the uterine tube. Cockshott and Lawson go on to state that if both uterine vessels are similarly enlarged an abdominal pregnancy secondary to rupture of a uterine pregnancy should be suspected. In only two of their eight patients were the placental inter-villous spaces demonstrated. The six remaining cases were associated with fetal death and the angiographic findings established the placental shutdown. The venous drainage was frequently into an ovarian vein. In the late arterial phase, opacification of the uterus may be noted. The identification of such a "uterogram" would clearly identify the relation of the placenta to uterus.

Wholey, in a review (1967) considered the abnormally high position of placental sinuses, the unusual participating arterial pattern and draining veins and a relatively small uterus as diagnostic of abdominal pregnancy.

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Multiple superficial gastric erosions due to Crohn's disease of the stomach. Radiologic and endoscopic diagnosis

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Abstract

A case of Crohn's disease involving the stomach and duodenum is presented. The patient had a four-and-a-half year history of ankylosing spondylitis. Double contrast radiography of the stomach and duodenum showed multiple superficial gastric erosions and a duodenal ulcer. There were typical changes of Crohn's disease in the terminal ileum. At endoscopy, numerous superficial erosions were seen in the stomach and duodenum and biopsies of the stomach showed granulomatous inflammation, consistent with Crohn's disease. These lesions are similar to those seen in the colon in the early stages of granulomatous colitis and it is likely that this represents the early stage of Crohn's disease in the stomach. With increasing application of double-contrast radiography and endoscopy, these lesions may be found more frequently.

Involvement of the upper gastrointestinal tract by Crohn's disease is relatively uncommon, occurring in only 2–3 per cent of patients with Crohn's disease (Kusakeioglu and Norton, 1967; Wilder and Davis, 1966). These patients invariably have evidence of Crohn's disease involving either the small bowel or the colon. Involvement of the stomach and duodenum is usually manifest by evidence of gastric outlet obstruction and in most reported cases, radiological studies show a narrow, rigid antrum and proximal duodenum. Discrete gastric ulcers or erosions have been demonstrated endoscopically in several reports (Beaudin, 1973; Cohen 1967; Elibol *et al.*, 1968; Kim *et al.*, 1973), but have never been convincingly demonstrated radiologically. Indeed, Marshak and Lindner (1970) state that the demonstration of discrete ulcers militates against the diagnosis of Crohn's disease of the stomach.

In this report, we document the unexpected finding of multiple superficial erosions in the stomach and duodenum due to Crohn's disease. The gastric lesions were demonstrated by double-contrast radiography and their nature confirmed endoscopically and histologically.

Case Report

A 21-year-old man complained of low back pain for five years. A diagnosis of ankylosing spondylitis had been made and he was treated with acetylsalicylic acid (ASA) for four

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and a half years. Nine months prior to admission, he developed epigastric pain, related to meals, aggravated by ASA and relieved by milk and Maalox. Six months prior to admission, barium studies were performed at another hospital and showed a duodenal ulcer. The ASA was therefore discontinued, but the pain and disability resulted in severe restriction of his activity. Thereafter, Indomethacin suppositories (100 mg BID) were prescribed. At approximately this time, he developed watery diarrhoea and urgency. This was occasionally accompanied by bright red blood in the stool. At the time of admission to hospital, he was having three to four semi-formed movements daily.

On physical examination, there was diffuse, mild, epigastric tenderness. He was tender to palpation over both sacro-iliac joints and there was limitation of flexion of the hips and the lumbar spine. Sigmoidoscopy revealed minimal inflammatory changes restricted to the anal canal.

The only abnormal haematological findings were a white blood count of 16,300/cu. mm with 83 per cent neutrophils and an ESR of 37 mm/hour. Tests for rheumatoid factor were negative.

Radiographs of the cervical, dorsal and lumbar spines were all normal. There were erosive and sclerotic changes involving both sacro-iliac joints, the symphysis pubis and both hip joints. A double-contrast colon examination was normal.

A double-contrast study of the stomach and duodenum was then carried out. Throughout the distal half of the stomach, there were numerous tiny collections of barium surrounded by a small radiolucent halo. These were interpreted as superficial gastric erosions. In addition, there was a well-defined ulcer crater in the center of the duodenal cap (Fig. 1A). The small bowel follow-through showed a rigid terminal ileum with a distorted and ulcerated mucosal pattern. The radiological diagnoses were:

(1) Crohn's disease of the terminal ileum;
(2) multiple superficial gastric erosions, probably due to Crohn's disease of the stomach;
(3) duodenal ulcer.

Endoscopy showed numerous 2–3 mm superficial erosions with raised erythematous margins (Fig. 1B) in the distal half of the stomach with areas of pale, normal gastric mucosa intervening. Erosions were also found in the duodenal cap. A good view of the duodenal ulcer was not obtained, as its base was covered with blood. Numerous biopsies were taken from the duodenum and the stomach.

Pathology

The gastric and duodenal biopsies showed extensive non-specific chronic gastritis with scattered, small, superficial erosions. In the base of one of these superficial ulcers in the antrum, there was an epithelioid granuloma of epithelioid histiocytes and giant cells (Fig. 2). Special stains (PAS and Burn's modification of Maxwell) (Whitehead, 1973) showed that these epithelioid histiocytes did not contain mucin. There were severe inflammatory changes in the duodenum, but no granulomata were found in the duodenal biopsies. The pathological diagnosis was granulomatous inflammation involving the stomach and probably the duodenum. The appearances were consistent with Crohn's disease and in view of the changes in the terminal ileum, a firm diagnosis of Crohn's disease of the stomach could be made.

DISCUSSION

In a recent review of Crohn's disease of the upper gastrointestinal tract, Beaudin *et al.* (1973), documented 18 cases of biopsy-proven Crohn's disease of the stomach. They had excluded cases without involvement of other parts of the bowel, since isolated granulomatous inflammation in the stomach may be a separate entity. Superficial erosions, such as those demonstrated in this patient, have not previously been demonstrated radiologically. The double contrast technique employed in this case differs significantly from the standard barium examination of the stomach (Kreel *et al.*, 1973; Laufer, 1975) and facilitates detection of superficial erosions because the dense barium adheres to the erosion which is then seen as a tiny spot of barium against a flat

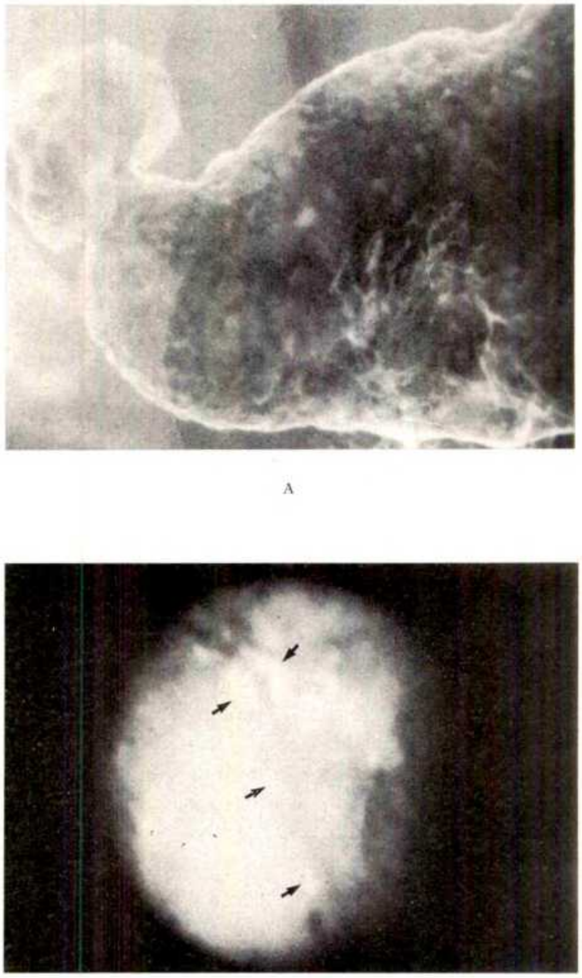

FIG. 1.

(A) Double-contrast study of distal stomach and duodenal cap showing numerous superficial gastric erosions and a duodenal ulcer.

(B) Corresponding endoscopic photograph showing numerous superficial erosions.

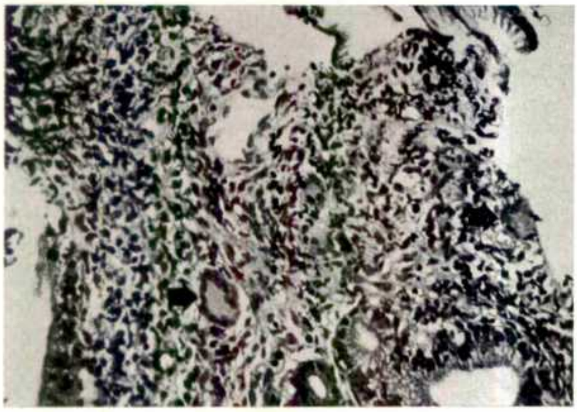

FIG. 2.

Portion of biopsy of antral mucosa showing inflammatory infiltrate in lamina propria with mononuclear cells, histiocytes and several epithelioid giant cells (arrows). H & E ×600.

background. This may be surrounded by a radiolucent halo caused by a mound of oedematous tissue around the erosion. We have demonstrated similar erosions by double-contrast radiography and endoscopy in other patients with vague digestive complaints and in patients with a history of ingestion of ethanol or ASA (Laufer *et al.*, 1976). Radiologically, the erosions in this patient are probably not distinguishable from these. However, the endoscopic finding of discrete erosions on a background of pale, normal mucosa, may be suggestive of Crohn's disease. We have demonstrated similar erosions on a background of normal mucosa in the colon by double-contrast radiography and colonoscopy in patients with granulomatous colitis (Laufer *et al.*, 1976).

It is likely that this patient's epigastric pain was related to his duodenal ulcer rather than to the superficial gastric erosions. These erosions probably represent an early, asymptomatic stage of Crohn's disease in the stomach and that progression to deeper ulcers, scarring and stenosis results in the more typical syndrome of gastric outlet obstruction. This would be consistent with Nelson's observations that patients with Crohn's disease of the stomach, duodenum or small bowel often present with advanced pathological changes and that the early stages of the disease are often asymptomatic (Nelson, 1969). With increasing application of a double-contrast technique to the examination of the stomach, this early stage of disease may be detected with increasing frequency in patients with Crohn's disease involving the small bowel or colon before the development of symptoms related to the upper gastrointestinal tract.

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Proceedings of The British Medical Ultrasonics Group

Aspects of grey scaling in ultrasonics

Abstracts of papers read at the Annual Meeting of The British Medical Ultrasonics Group held at the Winston Hall, University of Bristol, on Tuesday December 16, 1975

An introduction of grey scaling, by M. Halliwell.

Photographic aspects of grey scaling, by R. Railton, A. J. Hall and Patricia Morley.

Critical comparison of the diagnostic value of bistable and stored grey-scale display in routine ultrasound practice, by H. B. Meire.

An approach to quantitation of the grey-scale echogram, by J. C. Gore and S. Leeman.

Grey scaling in routine examinations of the first, second and third trimesters of pregnancy, by A. D. Christie and W. G. Millar.

Grey scale, a valuable tool in the differential diagnosis of hypertrophic cardiomyopathy, by J. Gehrke and S. Leeman.

Enhancement of displayed dynamic range by colour conversion of a stored grey-scale image, by H. B. Meire.

The assessment and management of carotid arterial disease using spectral analysis of the Doppler signal, by J. J. Baskett, M. G. Beasley, R. G. Gosling and D. E. Hyams.

Hydatidiform mole ultrasound diagnosis, by D. E. Beckly, A. Baird and F. G. M. Ross.

Ultrasound in the management of acute pancreatitis, by J. G. Duncan, C. W. Imrie and L. H. Blumgart.

Sonographic localization of intra-uterine contraceptive devices, by I. Watt, M. Halliwell, E. Margaret Watt and F. G. M. Ross.

Renal failure, by R. C. Sanders.

Ultrasound scanning in a radiotherapy department, by P. C.Badcock.

The assessment of abdominal lymph-nodes with ultrasound, by C. J. Tyrrell, D. O. Cosgrove and V. R. McCready.

AN INTRODUCTION TO GREY SCALING

By M. Halliwell

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Grey scaling is a term which has become a "key word" in diagnostic ultrasound. However, its meaning is somewhat ambiguous. This paper will attempt to provide a background to the techniques involved, the results produced and clarify some basic concepts. Consideration will also be given to the possible dichotomy between quantity and quality of the information contained in an ultrasonic B-scan.

PHOTOGRAPHIC ASPECTS OF GREY SCALING

By R. Railton, A. J. Hall and Patricia Morley

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Scan converters enable high resolution grey-scale pictures to be obtained. The ultrasound information is converted to a 625-line television format enabling a standard monitor to be used for the display. This leads to a consideration of the factors involved in obtaining a photographic record from the television monitor. The number of grey shades discernible in a picture is directly related to the ratio of white to black (brightness ratio). Typically, a monitor adjusted to give a visually pleasing display has a brightness ratio of 250:1 which is more than can be recorded on Polaroid 107 film (the usual recording medium). Two choices are available: a second monitor with a reduced contrast range can be used for photography with Polaroid 107, or negative film can be used with or without a second monitor. The processing, identification and handling of negative film is more complex but it yields high quality images. Polaroid 107 is convenient to handle and the result is readily available but a compromise in quality has to be accepted.

CRITICAL COMPARISON OF THE DIAGNOSTIC VALUE OF BISTABLE AND STORED GREY-SCALE DISPLAY IN ROUTINE ULTRASOUND PRACTICE

By H. B. Meire

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The bistable storage tube used in most ultrasound machines has no significant grey scale in its display and echoes which are below its threshold are not seen at all. In grey-scale display the higher amplitude echoes appear as brighter dots and the lower amplitude echoes as grey dots. In clinical use the grey-scale display has proven useful in detecting abnormalities in homogeneous organs like the liver and in detecting low-level echoes from structures such as clots within an aortic aneurysm. However, the grey-scale display also records any low-level artefacts or electronic interference in the ultrasound system and these may occasionally cause diagnostic confusion. The margins of cystic structures are never clear on this form of display, owing to the pulse length and the beam width.

It is therefore considered preferable to retain the bistable display for visualizing fluid filled structures such as cysts or the gall-bladder.

The choice of recording medium for the grey-scale image must also be considered and four media have been investigated. Polaroid film and electronically produced "hard copies" are both convenient in use but are expensive and have limited grey scale. 70 mm negative film and 35 mm positive film are less convenient in use owing to the delay in processing but have wider dynamic range and are much less expensive.

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AN APPROACH TO QUANTITATION OF THE GREY SCALE ECHOGRAM

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Grey-scale displays and their associated signal processing enhance anatomical recognition and tissue differentiation, but little quantitative information is derived from grey-scale images. The patterns of echoes displayed on a grey scale B-scan are derived from processing those signals produced by backscattering from fluctuations in the physical properties of tissues. It is shown that the envelope of the scattered signals, and therefore the pattern of echoes of a B-mode display contains quantitative information about fluctuations in the elasticity and density of the medium, and it is postulated that tissues may be characterized by a suitable analysis of this signal. A method of quantifying the spatial distribution of inhomogeneities to describe tissues is given in terms of measurements of the autocorrelation function of the received signals. Calculations of the autocorrelation function and power spectrum of the echoes from bovine liver are presented, and difficulties associated with such calculations are discussed, particularly the effects of scanner resolution.

GREY SCALING IN ROUTINE EXAMINATIONS OF THE FIRST, SECOND, AND THIRD TRIMESTERS OF PREGNANCY

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The introduction of grey-scale equipment as an additional facility to the standard Diasonograph 4102 (Nuclear Enterprises Ltd.) has enabled many intra-uterine features to be more easily recognized in routine examinations of the pregnant patient. For nearly two years, all patients in our area (approximately 1,200), who attend ante-natal clinics at Perth, have to be routinely examined by ultrasound at least three times during their pregnancy.

Initially these examinations were concerned with the establishing of gestational age by fetal crown-rump length, gestational sac size and biparietal measurement (BPD). In the later stages of pregnancy, monitoring of the BPD growth rate was believed to be indicative of satisfactory fetal growth. However, during the past 12 months, it has been possible to monitor many other intra-uterine features without increasing the overall examination time unduly. Grey scale displays enable rapid examinations of fetal spine, kidneys and heart to be made, and by correct orientation of the scanning plane, the display of a reproducible fetal trunk section. This section, in which the umbilical vein is an essential feature, can be found very quickly and its area measured by planimeter. In this way an additional growth parameter has been introduced routinely in examinations of all our patients. This dual system of monitoring BPD and FTA (fetal trunk area) has alerted us at a much earlier stage, of the fetus which is growing at an unsatisfactory rate, and has confirmed our previous impressions on the limitations of BPD measurements as an indication of growth and maturity.

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GREY SCALE, A VALUABLE TOOL IN THE DIFFERENTIAL DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY

By J. Gehrke and S. Leeman

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The echocardiographic diagnosis of hypertrophic cardiomyopathy (HOCM) is much facilitated by the use of the new cross-sectional cardiac imaging techniques, which provide also the additional advantage of accurately delineating the hypertrophied regions in the image plane. However, a differential echocardiographic sign is needed, since similar features are seen in other conditions, such as aortic stenosis. One such possibility is provided in the grey-scale display of the Siemens "Vidoson" mechanical scanner, now being used at Hammersmith Hospital for routine real-time B-scan echocardiography.

In a study of 50 patients presenting with clinical signs of left ventricular hypertrophy, the 20 HOCM cases were differentiated by a characteristic band of strong endocardial echoes of the interventricular septum.

A full discussion of the diagnostic procedure is given and a possible explanation for the distinctive sign described is discussed. A ciné film is presented, which underlines the ease with which the differential diagnosis may be made with appropriate grey-scale displays.

ENHANCEMENT OF DISPLAYED DYNAMIC RANGE BY COLOUR CONVERSION OF A STORED GREY SCALE IMAGE

By H. B. Meire

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The human eye can only appreciate about ten individual shades of grey but is capable of detecting a much larger number of colour shades. In theory, therefore, if one converts a grey-scale image into colour it should be possible to detect a larger number of smaller increments of amplitude. This should facilitate the detection of small areas of reduced echo amplitude in homogenous structures like the liver. This hypothethis has been investigated by feeding the video image from the scan converter of a Nuclear Enterprises Diasonograph into a colour conversion unit, designed and loaned by the Technical University of Delft. The use of a T.V. system also permits selective contrast enhancement.

Our results show that the system definitely does enhance low contrast levels, but its value is limited by the noise in the video signal and by non-uniformity of echo amplitude due to non-biological causes. These are principally the effects of imperfect swept gain characteristics and amplitude variations at different depths produced by the transducer beam characteristics. Further difficulties have been encountered in obtaining a true photographic record of the colour hues. It is felt that when these problems have been minimized, colour conversion may have some clinical value in certain limited clinical situations.

Proceedings of The British Medical Ultrasonics Group

THE ASSESSMENT AND MANAGEMENT OF CAROTID ARTERIAL DISEASE USING SPECTRAL ANALYSIS OF THE DOPPLER SIGNAL

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Using a Parks 805 10 MHz directional Doppler-shift velocimeter, signals from the supra-orbital and common carotid arteries have been obtained from 250 normal volunteers (5–88 years) and 73 patients (101 vessel segments —junction to ophthalmic) who underwent carotid arteriography. Signals were processed by a real-time spectrum analyser and the resultant sonogram digitized by a dedicated calculator. The sonograms change with age and disease. In particular, the ratio of the primary peak (peak A) to the secondary peak (B) falls to a mean value of 1·2 after the age of 65 years. However, comparison with angiography (53 normal, 48 diseased) showed that where the A/B ratio was less than 1·05 there was 88 per cent probability of disease present at the junction and if the A/B ratio was higher than 1·05 an 80 per cent probability of a normal vessel. The temporal artery occlusion test (TAOT) detected severe proximal disease. Furthermore, turbulence (defined as apparent sudden random increases in RBC velocities) was seen in the internal carotid in ten instances where disease was present at the junction and in 13 common carotids where, as direct carotid puncture was used, radiographic visualization of more proximal disease was not possible.

Lesions not detected were almost all minor and none were approaching haemodynamic importance (*i.e.* constricting the lumen by more than 50 per cent of the diameter).

It is therefore suggested that this method could be used:

(1) for non-invasive assessment as to the presence or absence of multifocal disease in the carotid arteries (or proximally) and hence decide the choice of arch or carotid arteriography;
(2) where multifocal disease is suspected, or where the Doppler sonogram is normal (excluding a haemodynamically important lesion) a conservative approach (*e.g.* anticoagulants) may prove to be more beneficial than invasive procedures;
(3) for the detection of the presence of an asymptomatic lesion by routine screening (*e.g.* before major surgery);
(4) as a simple means of following the course of normal ageing, or of disease, in this vessel segment.

HYDATIDIFORM MOLE ULTRASOUND DIAGNOSIS

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The experience of 25 cases is reviewed. In each case hydatidiform mole featured in the differential diagnosis of the abdominal compound B-scan. In 18 cases the subsequent diagnosis was confirmed as hydatidiform mole. In seven cases the final diagnosis was a condition other than mole. Ultrasound signs are stressed and the differential diagnosis is discussed.

ULTRASOUND IN THE MANAGEMENT OF ACUTE PANCREATITIS

By J. G. Duncan, C. W. Imrie and L. H. Blumgart

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Thirty-seven patients have been examined by ultrasound when symptoms or signs suggested the development of a pseudocyst following an attack of proven acute pancreatitis.

Pseudocysts occur particularly in males with a high alcohol intake in the 30–40 age group, and in cases of traumatic pancreatitis. Pseudocyst was diagnosed in 22 of the 37 cases. Four patients had multilocular cysts, three of which were shown to be communicating. Guided to a considerable extent by the ultrasound findings, laparotomy was carried out on 13 of the 22 patients, and surgical drainage was carried out in 12 cases. The remaining nine cases were monitored and showed steady regression. Cysts arising in the head of the pancreas may give rise to recurrent or persistent pancreatitis, and may be picked up by ultrasound. A further 11 patients showed an area of irregular absorption of ultrasound interpreted as an inflammatory mass (Bradley and Clements, 1974). Monitoring of these cases showed progressive resolution without cyst formation. Two of these cases required laparotomy—one developed an abscess, the other required a distal pancreatectomy.

The ability to distinguish between pseudocysts and inflammatory masses, and to demonstrate communication between multiple cysts, is of considerable help to the surgeon in management.

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SONOGRAPHIC LOCALIZATION OF INTRA-UTERINE CONTRACEPTIVE DEVICES

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Patients wearing IUCDs present for examination when the continued presence of the device within the uterine cavity is in doubt. This is due either to spontaneous expulsion, withdrawal of the threads into the uterus, or rarely perforation of the device through the uterine wall.

Ultrasonography is the only non-invasive and ionizing radiation free method of investigation, but accuracy rates for B scanning have varied from 89 per cent (Janssens *et al.*, 1973) to 100 per cent (Ianniruberto and Mastroberardino, 1972). The only A-scan report claims a 96 per cent accuracy (Winters, 1966). No study has reported the concurrent use of B+A scanning.

Twenty-two controls and 55 patients, in whom IUCDs had been inserted, were examined. From the A-scan an average ratio was made of the size of the uterine wall echoes to that from the uterine cavity. From the B-scan a blind assessment of the type of device present, if any, was attempted.

Localization. B-scanning achieved at a 92 per cent accuracy. The A-scan ratio of uterine walls echoes to cavity echo in controls was 7·19+SD 2·46 and in IUCD patients was 1·32+SD 0·41 ($p < 0{\cdot}001$). B and A-scans together achieved a 100 per cent accuracy.

Identification. Was correct in 65 per cent similar to other worker's experience (Janssens *et al.*, 1973).

It was concluded that ultrasound should be the initial investigation in localizing IUCDs within the uterine cavity and routine use of concurrent B+A scanning is accurate. Loop identification is unreliable but seldom necessary.

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RENAL FAILURE

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An important practical problem for the urologist is the management of the patient who has kidneys that cannot be seen adequately on intravenous pyelogram. Eighty-four patients in whom one or both kidneys were not adequately visualized on intravenous pyelogram have been examined by diagnostic ultrasound. Thirty-seven with bilateral non-visualization of the kidneys presented in renal failure. Most patients with renal failure had small end-stage kidneys (24); six had bilateral hydronephrosis and required surgical intervention. In two patients a combination of unilateral hydronephrosis due to uric acid stones and contralateral small end-stage kidneys were seen. Six patients with glomerulonephritis or acute tubular necrosis and individual patients with infantile and adult polycystic kidney and pre-renal azotemia were seen.

Of the 45 patients with unilateral non-visualization of the kidney, a positive diagnosis was possible by the combination of the ultrasonic and urographic appearances in all but one case. There were 24 patients with hydronephrosis, eight patients with infantile multicystic kidney, one with adult multicystic kidney, three with renal artery occlusion, one with renal vein thrombosis, one with perirenal abscess, one with a traumatized kidney and three with small end-stage kidneys. Ultrasonic discrimination between the different conditions was possible: hydronephrotic kidneys presented as enlarged cystic areas sometimes with septum, small end-stage kidneys were smaller than the normal kidney in length but retained the normal pelvic echo pattern, multicystic kidneys had several well defined cystic structures of varying sizes within them. In renal artery stenosis the kidney was normal but the IVP showed non-function. In perirenal abscess and trauma, a sonolucent collection adjacent to the kidney was seen.

ULTRASOUND SCANNING IN A RADIOTHERAPY DEPARTMENT

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Apart from its use in the detection and staging of tumours, ultrasound scanning offers particular advantages to the radiotherapist in treatment field planning. This application has not so far been much developed. At the Hammersmith Hospital, more than 300 patients undergoing radiotherapy treatment have been scanned and the technique has proved invaluable in the following contexts:

(1) chest-wall scanning, to confirm that the radiotherapy field adequately covers the involved region but avoids, as much as possible, the underlying lung;
(2) bladder scanning to estimate the extent of the tumour within the bladder, its penetration through the bladder wall and its extension through the pelvis;
(3) scanning of retroperitoneal tumours for accurate planning of radiotherapy treatment avoids damage to kidneys and gut;
(4) scanning of other tumours such as soft tissue sarcomata, thyroid, prostate and ovarian carcinomata and skin tumours.

In certain cases, heavy reliance is now made on the information from ultrasound scanning, for more conventional investigation would not allow imaging of the tumour-affected area in the treatment planes. On occasions carefully planned treatments based on conventional planning procedures have had to be modified on the strength of subsequent ultrasound scans, which revealed inadequate cover of the tumour or non-optimal treatment field positioning.

It would seem advisable that all radiotherapy departments acquire the necessary expertise and personnel to ensure that access to ultrasound scanning systems is easily available, both to increase the accuracy of defining the tumour-bearing area for treatment planning and to avoid other methods of investigation involving especially invasive techniques as these are often time-consuming, costly, unpleasant for the patient and occasionally hazardous.

THE ASSESSMENT OF ABDOMINAL LYMPH-NODES WITH ULTRASOUND

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Accurate detection and localization of enlarged lymph-nodes is of critical importance in a cancer department to enable rational treatment régimes to be planned.

Ultrasound has been found useful to assess abdominal nodes in the following circumstances:

(1) when a lymphogram cannot be performed;
(2) to show nodes in those sites not normally opacified by lymphography, *i.e.* the porta hepatis, the coeliac axis, the mesentery and the high para-aortic nodes above the origin of the thoracic duct;
(3) to determine the size and position of nodal masses for radiotherapy. Although the lymphogram and intravenous pyelogram may show the presence of abnormal nodes the extent of the nodal mass is often not defined. These masses can be visualized with ultrasound and using a projection system with appropriate magnification transposed on to radiotherapy planning films, and cross-sectional outlines.
(4) to assess the response of a tumour mass to radiotherapy or chemotherapy.

Scans were performed on the Royal Marsden Hospital prototype (Taylor and Hill, 1975; Taylor *et al.*, 1973) using multiple sequential transverse compounded sections and longitudinal sector scans. The importance of scanning in two dimensions was stressed.

The normal anatomy in the upper para-aortic region is complicated. The great vessels must be identified because of the close relation of the lymph-nodes. The usual appearance of a nodal mass is an area of decreased echoes in relation to the Aorta or IVC which may be displaced or compressed.

A primary carcinoma of the pancreas may give very similar appearances to a nodal mass in the para-aortic region.

This is a non-invasive, repeatable technique which has been found very useful in this area in conjunction with lymphography and other diagnostic methods.

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1976, *British Journal of Radiology*, *49*, 733 AUGUST 1976

Short communication

OER reduction with high-energy nuetrons

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We recently reported that neutrons produced by 80 MeV deuterons bombarding a thick beryllium target have an $\mathrm{OER}=1{\cdot}3\pm0{\cdot}2$ measured with *Vicia* seedlings (Harrison *et al.*, 1975). This study has been extended to include additional measurements with other high-energy neutron sources (Table I). The mean neutron energies were obtained from time-of-flight energy spectra; these spectra and other physical and dosimetric data will appear elsewhere (Harrison *et al.*, 1976).

The experiments to measure the OER for *Vicia* were performed as described in the previous correspondence (Harrison *et al.*, 1975). OER is defined as the ratio of D_{50} values under hypoxic and oxic conditions. The OER was 2·6 in control experiments with 250 kV X rays, demonstrating that an adequate degree of hypoxia was achieved.

TABLE I

NEUTRON SOURCES

Accelerator	Primary beam	*Vicia* dose-rate (rad/min.)	Mean neutron energy (MeV)
U.S. naval research	35 MeV deuteron	60	15
Fermilab	66 MeV proton	15	22
University of Maryland	80 MeV deuteron	13	32
University of Maryland	101 MeV proton	13	50

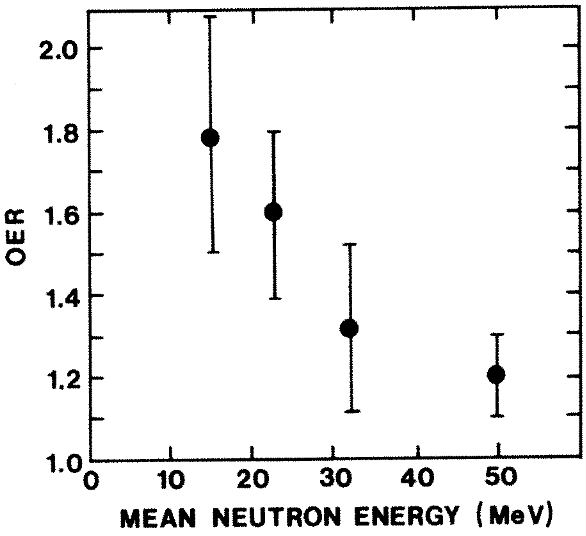

FIG. 1.

OER as a function of mean neutron energy.

The neutron OER values, with standard errors, are shown as a function of mean neutron energy in Fig. 1. The choice of mean energy as a radiobiological parameter is arbitrary, and is meant only to describe the neutron beams. The data suggest a significant reduction in OER as the mean energy is increased above 25 MeV; the probability that the observed correlation of decreasing OER with increasing neutron energy occurred by chance is 0·05. The implications of these results for cancer therapy are clear since the original rationale for clinical trials with neutrons was centred almost exclusively on reduced OER.

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Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

A CAUSE OF NON-OPACIFICATION OF THE GALL-BLADDER: TREATMENT WITH SECHOLEX

About 2–4 per cent of normal gall-bladders fail to concentrate oral contrast medium. Thus the investigation gives a false-negative result. The oral contrast media for gall-bladder visualization are absorbed through the intestine combined with a low-molecular protein (Y) transported to the liver, and again combined with another protein (Z) and finally excreted in the bile. (Sokoloff *et al.*, 1973). The excretion is similar to that of phenolphthalein derivates (bromsulphothalein) and the natural bile acids.

An anion exchange resin, Secholex (polidexine, formerly described as DEAE-Sephadex or PDX-chloride) has recently been introduced for the treatment of hypercholesteraemia and the prevention of coronary heart disease (Howard and Courtenay Evans, 1974). With a dosage of 15 g per day the mean monthly plasma cholesterol level will be decreased by 10–18 per cent of the pre-treatment values (Gustafson and Lanner, 1974). The mechanism of action of this drug is to bind bile acids in the intestine, thus facilitating their increased faecal excretion. Since cholesterol is the precursor of the bile acids the body content of cholesterol (including plasma cholesterol) is consequently reduced (Howard and Hyams, 1971). In theory, therefore, one could reasonably infer that Secholex might disturb the absorption of oral cholecystographic contrast media and lead to difficulty in the interpretation of cholecystograms. Furthermore, patients with high plasma cholesterol values are often obese and thus candidates for gall-bladder disease.

Twenty-one healthy adults aged 20–40 with normal previous cholecystograms served as the material for this study. Cholecystography was performed using a double dose of Solu-Biloptin (calcium ipodate) by the routine method. Each received either 10 or 20 g of Secholex orally for two days before repeat cholecystography.

All those receiving 20 g of Secholex per day showed total non-opacification of the gall-bladder and those receiving 10 g per day showed little or no visualisation of their healthy gall-bladders. Thus it appears that Secholex causes the sequestration of Solu-Bilobtin and apparently also other gall-bladder contrast media, as well as natural bile acids. This finding should be taken into account in cholecystography in patients on Secholex treatment. This is apparently valid also for the two other bile acid sequestrants on the market, cholestyramine and colestipol.

Yours, etc.,
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THE EDITOR—SIR,

A NUMERICAL INDEX OF GAMMA-CAMERA UNIFORMITY

The image of an evenly distributed source of radioactivity is often used as a means of checking that the response of a gamma-camera is uniform over a large fraction of its crystal area. This image is generally termed a flood field image. If a computer link is available, images may be collected as digital arrays. It is generally observed that the resultant image is non-uniform due to such factors as variations in sensitivity over the detecting area (Anger, 1967), spatial displacement of the position of events (Spector *et al.*, 1972) and non-linearity of channel widths in analogue to digital converters. Uniformity correction is normally carried out by dividing each element of the clinical image array by the corresponding element in the flood field image array. This method of uniformity correction compensates only for differences in sensitivity over different parts of the crystal face and non-linearity of analogue to digital converters but takes no account of spatial distortions (Ashare *et al.*, 1975; Spector *et al.*, 1972).

Whether or not uniformity correction is carried out, it is important to ensure that the gamma-camera response to a uniform distribution of radioactivity is stable over long periods of time. Visual inspection of the flood field image may reveal changes which depend to a large extent on the experience of the observer. A method is presented here for numerical analysis of the flood field image.

The variance, V_t, of the array elements within a flood field image may be expressed as the sum of two components.

$$V_t = V_r + V_s \quad . \quad . \quad . \quad . \quad (1)$$

where V_r is the variance associated with the random nature of the detection of events from radioactive sources, and V_s is the variance associated with the systematic errors introduced by non-uniformity of the gamma-camera. The total sample variance is given by

$$V_t = \sum_{i=1}^{N} (X_i - \overline{X})^2 / N \quad . \quad . \quad . \quad . \quad (2)$$

where X_i is the number of counts in element i, and N is the number of elements in a hexagon which covers the useful portion of the flood field image and excludes the extreme edges which are clinically unreliable ($N = 1{,}756$).

The best estimate of V_r is the mean number of counts per element, $\overline{X}$. To a first approximation the fractional systematic error introduced by the non-uniformity of the gamma-camera may be written

$$K = V_s^{\frac{1}{2}} / \overline{X} \quad . \quad . \quad . \quad . \quad (3)$$

where K may be called the "uniformity index". It may be evaluated using equation 1 to eliminate V_s. Hence:

$$K = (V_t - \overline{X})^{\frac{1}{2}} / \overline{X} \quad . \quad . \quad . \quad . \quad (4)$$

The above expression for K is independent of the number of counts collected and the random error associated with the flood field. This is not the case if the uniformity of the system is expressed as the total variance V_t. It should be noted that the above comments are only valid if non-linear factors, such as dead time losses, are small and may therefore be neglected.

Figure 1 demonstrates that the standard deviation of the estimation of the uniformity index shows stochastic convergence towards zero with increasing number of counts per element.

Correspondence

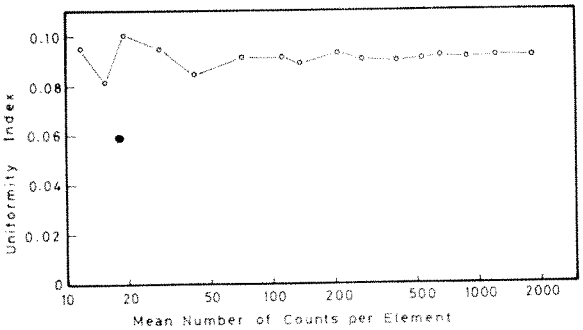

FIG. 1.

The variation of the uniformity index with mean number of counts per element for a series of measured flood fields.

The determination of the uniformity index has been in daily use for the last two months. A 3 mCi ^{99}Tc^{m} flood tank, 34 cm in diameter, is placed on top of a medium resolution, low energy, parallel hole collimator and yields a count rate of about 5,000 counts second^{-1}. After a total of 3×10^6 counts have been collected, a computer program written in Fortran takes about 20 seconds to evaluate the uniformity index. A mean value of the index obtained from 50 daily determinations was $0{\cdot}086 \pm 0{\cdot}006$.

The simple technique described here is a useful procedure in the routine quality control of a gamma-camera and will detect quantitative changes in the performance of the system more readily than by visual observation.

We should like to thank Mr. J. R. Corfield for his helpful interest in this work and his critical comments of the manuscript.

Yours, etc.,
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THE EDITOR—SIR,

THE IRREGULAR RENOGRAM

In many cases the descending part of the renogram, normally a smooth concave curve, is distorted by irregularities (Winter, 1963; Harvey and Keeling, 1969; Britton and Brown, 1971). Britton and Brown (1971) relate these irregularities to slight and transient renal ischaemia, causing a transient reduction in urine flow in the kidney, with relatively large increases in Hippuran concentration brought about by a disproportionately increased fractional reabsorption of salt and water in the proximal tubule. By this mechanism a rise in the descending part of the renogram can be explained.

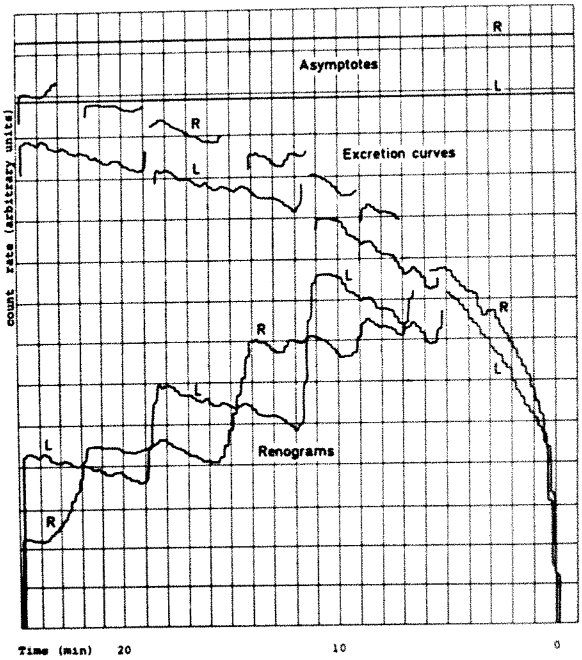

FIG. 1.

Parts of a renogram (lower pair of curves) recorded during a period of zero urine flow must be exact but displaced replicas of the corresponding parts of two excretion curves each representing the amount of Hippuran already cleared by one kidney. In this figure the excretion curves have been constructed fitting successive fragments of the renogram by vertical translation to the already existing initial part of the curve. The resultant curves fulfil the theoretical requirement that they approach their asymptotes exponentially and with an equal time constant ($\tau = 14$ minutes). Note: The renogram has been recorded from right to left.

Though this theory may be appropriate to explain most irregularities, it seems not applicable to renograms of the type shown in Fig. 1. In our experience there are many renograms with irregularities in the third phase. About 5 per cent of these are of the type presented, characterized by rising parts in the third phase which run parallel with the extrapolated initial part of the curve, *i.e.* with the curve that would be obtained if all extracted Hippuran remained in the kidney. To explain this phenomenon it seems that the initial conditions must be maintained or restored during a rise, *i.e.* an unimpaired blood supply but with the absence of any urine flow. In terms of the ischaemia theory this would mean that a complete cessation of urine flow is induced by a practically imperceptible decrease of the renal blood flow.

In conclusion, while for most irregularities in the third phase of the renogram the ischaemia theory would offer a satisfactory explanation, there is a particular type of renogram where this theory might be inadequate.

It is more likely that a temporary cessation of urine flow (whatever the cause) would explain the appearance of such renograms.

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THE EDITOR—SIR,

RADIOACTIVE CONTAMINATION HAZARD FROM PATIENTS

The hazard of contamination and cross contamination associated with in-patients who have been injected with radioactive material for diagnostic purposes (such as imaging) is sometimes not fully appreciated.

The Code of Practice (H.M.S.O. 1972, section 6.6.1) states that "where only a few patients are involved, each containing less than 10 microcuries, no special safety precautions in the wards and clinics are necessary . . . ". Hospitals using radioisotopes for organ imaging frequently administer activities in excess of 1 mCi. After these patients are returned to the ward (not necessarily in the same hospital), urine is sometimes collected and sent for assay with no indication of any radiation hazard.

The quantity of activity appearing in the 24-hour urine from a patient initially injected with 10 mCi of ^{99}Tc^{m} may be 0·5 mCi so that spillage or incontinence can easily produce a contamination hazard with surface activities many times greater than the derived working limit of 10^{-4} μCi/cm^2. Furthermore, ignorance of the radioactivity of a urine sample can interfere with a specific biochemical test, for example the measurement of cortesol secretion rate using tritium.

It is important that patients who have received such levels of radioactivity should be easily identifiable to enable nursing staff to appreciate that a hazard exists in the event of incontinence. Instructions (extracted from the local rules) can be issued to the Nursing Officer in charge of wards summarizing the precautions to be taken in such circumstances, and indicating the length of time for which these special provisions should apply. One means of identification could be a small yellow wrist band displaying a black trefoil sign and the date on which the radioisotope was administered: the wrist band would be removed after a specified period. Once the patient has been identified it is a relatively easy matter to ensure that any urine samples sent to other departments are labelled as radioactive material.

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THE EDITOR—SIR,

FORMULAE FOR CALCULATION OF 50 PER CENT DEPTH DOSE AND LINEAR ABSORPTION COEFFICIENT IN WATER OF COBALT-60 γ RAYS

In telecobalt therapy, data for central axis percentage depth doses can be used for the calculation of dose distributions in an irradiated volume, and hence for the calculation of the integral absorbed dose.

The integral absorbed dose can be calculated by the formula of Mayneord, modified by Johns (1964):

$$\Sigma = 1{\cdot}44\, D_0\, A\, d_{\frac{1}{2}}\, [1 + 2{\cdot}88\, (d_{\frac{1}{2}}/f)]\, [1 - \exp(-0{\cdot}693 d/d_{\frac{1}{2}})] \quad (1)$$

where Σ = integral absorbed dose
D_0 = dose on the skin
A = area of equivalent field
f = source–skin distance
d = thickness of the patient
$d_{\frac{1}{2}}$ = depth of 50 per cent dose on the central axis

The value of $d_{\frac{1}{2}}$ depends on the size of the field and the source–skin distance (SSD). A formula for calculating $d_{\frac{1}{2}}$, from the side L of the equivalent square field and the SSD has been derived using the percentage depth-dose data published in *Supplement No. 11 of the British Journal of Radiology* (1972). In addition a relationship between linear absorption coefficient K, SSD and L has been calculated.

METHOD

The central axis percentage depth dose for ^{60}Co radiation is exponential beyond the first 5 cm below the phantom surface (Pfalzner, 1960). The general formula which is applicable is

$$D_x = D_0 \exp(-K.x) \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where D_x = central axis percentage depth dose at depth x
D_0 = extrapolated value of percentage depth dose at $x = 0$
K = linear absorption coefficient of the radiation beam in tissue
x = depth below the surface

The values of K and D_0 for all field sizes and values of SSD can be obtained by extrapolating, with the method of least squares, straight lines with the general formula:

$$Y = a + bx \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where $Y = ln$ of central axis percentage depth dose
and x = depth

Here, $a = ln\, D_0$, and $b = -K$. Values of $d_{\frac{1}{2}}$ can be obtained by putting in formula (2) $D_x = 50$ and $x = d_{\frac{1}{2}}$.
We then have

$$d_{\frac{1}{2}} = \frac{(ln\ 50 - ln\ D_0)}{-K} \quad . \quad . \quad . \quad (4)$$

The dependence of $d_{\frac{1}{2}}$ on SSD and on L has been evaluated, calculating with the method of determinants the parameters of a triple regression with a general formula (Lison, 1961).

$$Y' = a' + b'W + c'Z$$

where $Y' = ln\, d_{\frac{1}{2}}$
W = source-skin distance f
$Z = ln\, L$

In the same way, the dependence of $ln\ K$ on SSD and on L has been determined. The significance of the regression coefficients for the straight line and the significance of the multiple regression have been evaluated using Fisher's test of significance $F(K)$ as indicated by Lison (1961). The calculations have been made with a PDP-8 computer, using programs written in Focal.

RESULTS

In Columns 2, 3, 4 and 5 of Tables I, II and III are given the values of D_0, K and $F(K)$ and $d_{\frac{1}{2}}$ derived from percentage depth-dose data between 5 and 20 cm depth from

TABLE I
SSD 50 CM

1	2	3	4	5	6	7
Field (cm × cm)	D_0	K (cm^{-1})	$F(K)$	$d_{\frac{1}{2}}$ (cm)	K calculated with formula (6) (cm^{-1})	$d_{\frac{1}{2}}$ calculated with formula (7) (cm)
4×4	108·1	0·0903	809,497·08	8·5	0·0897	8·5
5×5	109·6	0·0888	470,234·97	8·8	0·0881	8·8
6×6	110·6	0·0872	890,090·30	9·1	0·0865	9·1
7×7	111·1	0·0855	424,456·09	9·3	0·0850	9·4
8×8	111·2	0·0837	489,671·99	9·5	0·0834	9·6
10×10	111·2	0·0806	681,050·50	9·9	0·0805	10·0
12×12	110·1	0·0771	253,499·07	10·2	0·0776	10·3
15×15	108·8	0·0729	198,817·93	10·7	0·0735	10·7
20×20	107·3	0·0676	306,834·60	11·3	0·0671	11·3

TABLE II
SSD 60 CM

1	2	3	4	5	6	7
Field (cm × cm)	D_0	K (cm^{-1})	$F(K)$	$d_{\frac{1}{2}}$ (cm)	K calculated with formula (6) (cm^{-1})	$d_{\frac{1}{2}}$ calculated with formula (7) (cm)
4×4	109·6	0·0865	188,973·30	9·1	0·0863	8·9
5×5	110·7	0·0848	251,739·85	9·4	0·0848	9·3
6×6	111·8	0·0833	313,205·06	9·7	0·0832	9·6
7×7	112·0	0·0814	320,259·14	9·9	0·0817	9·8
8×8	112·2	0·0797	358,329·08	10·1	0·0803	10·1
10×10	111·9	0·0766	370,560·00	10·5	0·0774	10·5
12×12	111·1	0·0735	261,981·69	10·9	0·0746	10·8
15×15	110·3	0·0699	297,465·05	11·3	0·0707	11·2
20×20	108·8	0·0648	372,233·27	12·0	0·0646	11·8

Tables 6.1, 6.2 and 6.3 of *Supplement 11*. In Columns 6 and 7 are listed the values of K and $d_{\frac{1}{2}}$ calculated with the following formulae:

$$ln\ K = -(2{\cdot}1444 + 0{\cdot}0039f + 0{\cdot}0182\,L) \qquad . \quad . \ (6)$$

$$ln\ d_{\frac{1}{2}} = (1{\cdot}6656 + 0{\cdot}0047f + 0{\cdot}1736\ ln\ L) \qquad . \quad . \ (7)$$

The values of K and $d_{\frac{1}{2}}$ calculated with formulae (3) and (4) differ very little from those calculated with formulae (6) and (7); the differences between each pair of values is always less than 2 per cent, except K for the field 20×20 cm and 80 SSD where the difference is 2·3 per cent.

Using formula (7), $d_{\frac{1}{2}}$ may be calculated for use in formula (1) to calculate the integral absorbed dose.

It is worth noting that using formulae (6) and (7) together, it is possible to calculate the axial percentage depth dose for depths greater than 5 cm, for any given field size and SSD, using the following formula:

$$D_x' = 50 \exp\left[-K(x' - d_{\frac{1}{2}})\right] \qquad . \quad . \quad . \quad . \ (8)$$

1976, *British Journal of Radiology*, *49*, 738–739

TABLE III

SSD 80 CM

1	2	3	4	5	6	7
Field (cm × cm)	D_0	K (cm^{-1})	$F(K)$	$d_{\frac{1}{2}}$ (cm)	K calculated with formula (6) (cm^{-1})	$d_{\frac{1}{2}}$ calculated with formula (7) (cm)
4×4	110·1	0·0803	362,572·39	9·8	0·0799	9·8
5×5	111·4	0·0787	246,567·43	10·2	0·0784	10·2
6×6	112·4	0·0772	252,371·77	10·5	0·0770	10·5
7×7	112·8	0·0756	198,427·74	10·8	0·0756	10·8
8×8	113·0	0·0740	247,162·50	11·0	0·0743	11·1
10×10	112·9	0·0711	239,251·31	11·5	0·0716	11·5
12×12	112·5	0·0685	202,395·74	11·8	0·0691	11·9
15×15	111·8	0·0653	192,397·36	12·3	0·0654	12·3
20×20	110·5	0·0611	130,544·73	13·0	0·0597	13·0

where x' = the desired depth
D_{x}' = desired percentage depth dose

The differences between the values of central axis percentage depth dose at depths more than 5 cm, calculated with formula (8) and those reported in *Supplement 11*, are always less than 2 per cent for each pair of values.

Yours, etc.,

F. DI PIETRANTONJ.

Centro Oncologico e di Medicina Nucleare,
"Francesco Angelini",
Ospedale Specializzato Regionale,
Ancona 60100, Italy.

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PFALZNER, P. M., 1960. Graphical presentation of axial depth dose values, *British Journal of Radiology*, *33*, 198.

THE EDITOR—SIR,

A PROPOSAL FOR SI PREFIXES

The introduction of SI units represents on the whole commendable progress towards a practical and universal system of units of measurement and associated unit and quantity symbols. While it is clear that a very large effort has gone into the documentation of the International System, it is unfortunate that no attempt has been made to rationalize the currently used prefixes denoting decimal multiples and submultiples of SI units. The names of these prefixes and corresponding symbols (Table I) appear to be arbitrary and unsystematic, although—or probably because—some of them are widely accepted in popular usage in many countries.

TABLE I

THE PRESENT SI PREFIXES

Power of 10	Positive		Negative	
	Name	Symbol	Name	Symbol
1	deca	da	deci	d
2	hecto	h	centi	c
3	kilo	k	milli	m
6	mega	M	micro	μ
9	giga	G	nano	n
12	tera	T	pico	p
15	peta	P	femto	f
18	exa	E	atto	a

These names have, however, certain obvious defects; there is no general, consistent relation to the magnitude of the power of ten involved, the positive and negative powers are quite unrelated, and the choice of symbols follows no systematic principle. It remains, in fact, something of a minor mystery how and by whom such terms as "pico", "femto", "atto" and "tera" were invented! Only recently, two entirely new terms, "peta" and "exa," have suddenly been revealed to the world of science.

Such a situation is not consistent with the aims of SI to provide a unified, and as far as possible rational, practical system of measurement units. Obviously what is needed in the case of these prefixes is a basic principle so that the names of the prefixes relate directly to the magnitude of the power of 10, with negative and positive powers clearly distinguished yet related, and with symbols systematically and consistently related to the name and sign of the prefix.

There are probably various ways of setting up such a scheme, and it is the purpose of this note to suggest two possible methods of doing so (Table II). It will be seen that the meaning of the terms is self-explanatory, that the

TABLE II

SUGGESTED NEW PREFIXES FOR SI UNITS

Power of 10	Positive			Negative		
	Name (a)	Name (b)	Symbol	Name (a)	Name (b)	Symbol
2	plu-Do	Bi-pos	D or B	mi-do	bi-neg	d or b
3	plu-Tri	Tri-pos	T	mi-tri	tri-neg	t
6	plu-Sexa	Hexa-pos	S or H	mi-sexa	hexa-neg	s or h
9	plu-Nona	Nona-pos	N	mi-nona	nona-neg	n
12	plu-Dodeka	Dodeka-pos	DD	mi-dodeka	dodeka-neg	dd
15	plu-Pentdeka	Pentdeka-pos	PD	mi-pentdeka	pentdeka-neg	pd
18	plu-Octdeka	Octdeka-pos	OD	mi-octdeka	octdeka-neg	od

suggested symbols relate systematically to the names, and present no problems to typists or printers. It is also clear that additional names can be easily formed on the same principles without requiring a secret conclave of wordsmiths! For simplicity in writing when not employing symbols only, the terms could be used without the syllables plu, pos, etc., indicating positive powers by a capital initial, negative ones by a lower case. It may be said that it would be difficult to replace terms now in common use, such as hecto, centi, milli, kilo, micro and mega, with any of these suggested here. While this may be true to some extent in popular usage, it should not be so in scientific usage where new agreed terms have frequently displaced, or are in the process of replacing older, often well-established ones, such as Fahrenheit, pound (-force) per square inch, or even millicurie, etc. In any case, for names denoting powers of ± 6 or greater the existing terms have hardly entered popular usage, and a switch to new ones could readily be accomplished. It will be seen that no new terms are suggested to replace "deca" and "deci", and these could well be dropped from scientific usage altogether.

Concerning the symbols, it will be noted that n retains its meaning, and that the only symbols already in use with a new meaning would be T and h, the latter replacing the symbol for "micro" which at present has also the undesirable feature of being the only one requiring a Greek letter. It is clear that the adoption of a mnemonic system of prefixes for SI units such as suggested here would be highly desirable.

Yours, etc.,
P. M. PFALZNER.

The Ontario Cancer Foundation (Ottawa Clinic)
Ottawa, Canada.

THE EDITOR—SIR,

VAN BUCHEM'S DISEASE

I found Dr. Owen's article (B.J.R., 1976) most interesting, but Table II is a little misleading. The skull is sclerotic in more than half the reported cases of diaphyseal dysplasia; sparing of the mandible and facial bones in osteopetrosis is relative rather than absolute.

Yours etc.,
D. SHAW

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University College Hospital,
Gower Street,
London WC1E 6AU

REFERENCE

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THE EDITOR—SIR,

BONE CHANGES IN INTRAHEPATIC BILIARY ATRESIA

We were very interested in reading the article entitled "Bone Changes in intrahepatic biliary atresia" (Raghavendra and Genieser, 1976). However, this report concerns only part of the changes which have already been reported in this syndrome. Indeed, vertebral anomalies have also been observed. The few cases found in the literature by the authors is also very surprising (Alagille *et al.*, 1975).

Yours, etc.,
D. ALAGILLE.

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I.N.S.E.R.M.U 56,
Hôpital d'Enfants,
94270 Bicêtre, France.

REFERENCES

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RAGHAVENDRA, B. N., and GENIESER, N. B., 1976. Bone changes in intrahepatic biliary atresia. *British Journal of Radiology*, *49*, 179–181.

THE EDITOR—SIR,

MUST RADIOLOGISTS DO ALL THE REPORTING?

I was pleased to see this complex and somewhat "sticky" problem brought into the open. It was discussed in the American literature a few years ago (Addington *et al.*, 1972; Correspondence, 1972). The well-known arguments noted by Dr. Emrys-Roberts (1975) and many other equally good points will not be repeated here.

I personally believe the problem is being looked at too narrowly. If one is trying to utilize radiologists' time efficiently, then ALL of the duties which they traditionally perform in running X-ray departments must be considered together. Only then can a comprehensive analysis be made in order to decide where to "cut corners" while doing the least potential harm to the patients. For instance, to start with, unecessary X-rays must be discouraged (there are other good reasons for this too) and we all know that many are requested every day (Middlemass, 1971), especially skull films (Roberts and Shopfner, 1972; Bell and Loop, 1971; Hayes and Shopfner, 1973). Then, perhaps in some smaller centres, it would be more practical to eliminate time consuming special procedures (they could be done in more specialized centres). Also, as is now being tried in the United States and Japan, specially trained radiographers might be allowed to perform some screening procedures (Lewicki, 1975). Professional, non-physician departmental administrators might save time (and perhaps do a better job in some areas) for busy radiologists who must also administrate. No possibility should be overlooked; delegating film reading to others is not the only way to save the radiologists' time.

Finally, as to my own view regarding the interpretation of X-rays, although it may be considered heresy coming from a radiologist; if a specialist clinician is as knowledgeable or more knowledgeable in some areas of X-ray interpretation than the available radiologist, the radiologist should not feel duty-bound to read such films if he is already overburdened and the clinician is willing to accept the responsibility. This situation can arise in large hospitals with specialists, such as neurosurgeons and orthopaedists, when only an overworked general radiologist is available and his sub-specialty interests lie elsewhere. I will admit, without shame, that I have met neurosurgeons who know more about neuroradiology than I do, and orthopaedic surgeons who know more about fragment rotation, muscle pull, etc., in fractures than I do. Obviously the situation will vary at each centre and with the personalities involved.

Specifically, however, regarding casualty work and general practitioners reading X-ray films, the fact is that if more people view the same films (double reading), fewer errors will be made (Galasko and Monahan, 1971). Also, I believe, the more experienced the interpreter, the fewer the errors. This suggests that, for the present at least, radiologists should be involved in the interpretation of these films in most, if not all, cases as the primary or at least a secondary reader. Perhaps in the future, specialty training for general practitioners and casualty room physicians could include X-ray interpretation so these physicians can be used for primary film reading. They, in fact, may be in a better position to co-ordinate the radiographs with the clinical findings. They always (I hope) examine the patient; the overburdened radiologist too frequently does not have such an opportunity.

Finally, let us not forget that every effort should be made now to increase recruitment into radiology as there is a considerable timelag between recruitment and qualification (Brogdon and Moseley, 1975).

Yours, etc.,
S. P. Bohrer.

Professor and Head of Radiology,
University of Ibadan,
Ibadan, Nigeria.

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The Editor—Sir, C576A E37

Must Radiologists do all the Reporting?

Dr. M. J. Brindle, in the British Journal of Radiology of March 1976, feels that radiologists should, in order to devote more time to practical procedures, administration, and participation in ward rounds, give up routine reporting of films. I find it difficult to see how one can control the quality of work from one's department without seeing the films. Likewise, unless the sequence of films of a patient's progress have been seen, I fail to see how one can advise on the further investigation of the patients referred.

The issuing of a report takes, perhaps, an average of one to two minutes of the radiologist's time, and should provide an easily assimilated communication between radiologist and clinician. Discussion will take considerably longer than this, whether in ward or department, and without a written report, may have to be repeated *ad nauseam*. The effect of non-reporting of films will be an increase in the number of investigations and of radiation dosages. The responsibility of the radiologist is not only to perform an investigation, but to ensure that all the information is extracted from the films, and the discipline of reporting helps to ensure this.

To see where relatively unregulated investigations can lead, one has only to look at a busy accident department. In hospitals with such a department, the work of the X-ray department can be 50 per cent from this source alone. Attempts to limit this load always seem to be frustrated by the 'medico-legal' argument. The majority of trauma cases, (about 85 per cent), have negative X rays anyway, and the interpretation is usually not difficult, especially in a clinical situation. Also, by the time the radiologist sees the films, the management of the patient has been decided. There is no reason why an orthopaedic or casualty consultant should not check the trauma films from casualty. The radiologist could see films of patients admitted, those with non-traumatic conditions, and where specially requested.

I suggest that this system would reduce the radiologist's workload, with the minimum of damage, and would leave the radiologist with his bird's-eye view of patients going through the hospital, which is one of his most interesting and valuable assets.

The question of limiting the vast number of unnecessary X-rays arising from Accident Departments is one which will have to be tackled by the medical and legal professions—but this is a different matter.

Yours, etc.,
C. P. Cooper.

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London E11 1NR.

1976, *British Journal of Radiology*, *49*, 741–742

AUGUST 1976

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meetings announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

A Conference on Cancer of the Uterus

To be held in Kladovo, Yugoslavia, September 22–24, 1976.

Organized by the Working Party on the Use of Radionuclides and Afterloading Techniques in the Treatment of Cancer of the Uterus in Developing Areas and The Yugoslav Assocation of Radiology and Nuclear Medicine.

Topics will include:

Cancer of the Uterus as a Public Health Problem throughout the World.

Organization of Health Care in Cancer of the Uterus.

Etiology, Prevention, Pathology.

Changing Patterns, Endometrium and Cervix.

Methods of Early Diagnosis.

Treatment, surgical.

Treatment, radiation.

Intracavitary Methods: Afterloading, High Intensity Remote Loading, Combination with External Radiotherapy, Description of Available Devices for Afterloading and Remote Loading.

Bowel Reactions.

Radiobiology of High Intensity Remote Loading.

Dose Considerations in Remote Loading.

Registration to: Zlatko Merkas, M.D., Professor of Radiology, Institute of Radiology, Paterova ulica 14, 11 000 Belgrade, Yugoslavia.

Joint Radiological Meeting

To be held on September 24–25, 1976 at Leeds University Arts Block.

Sponsored by The Royal College of Radiologists and the British Institute of Radiology.

Details of the programme and registration from The General Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

David Anderson-Berry Prize

A David Anderson-Berry silver-gilt medal, together with a sum of money amounting to not less than £100 (£100 = U.S. $200), will be awarded by the Council of the Royal Society of Edinburgh during 1976. The Prize will be awarded for recent work on the effects of X rays and other forms of radiation on living tissues. Published work will be taken into consideration if submitted to the Society with the application.

In addition to direct application for the prize, proposals may be made on behalf of others.

Applications and proposals must be in the hands of the General Secretary, Royal Society of Edinburgh, 22/24 George Street, Edinburgh EH2 2PQ, Scotland, not later than September 28, 1976.

A Symposium on Radioisotopes in Cardiology

Jointly organized by The British Institute of Radiology and the British Cardiac Society will be held on Wednesday, September 29, 1976, at the Greenwood Conference Centre, Guy's Hospital.

Registration fee: £9·50 including lunch, morning coffee and afternoon tea.

Further details and registration forms will be available from The Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Attendance may be limited and registrations will be accepted in the order they are received.

European Symposium on Gynaecological Cancer

This meeting to be held at the Hilton Hotel, Athens, on October 7–8, 1976, under the auspices of the European Association of Radiology.

Further information from: EAR Symposium on Gynaecological Cancer, Areteion Hospital, 76V as. Sophias Avenue, Athens 611, Greece.

8th Congress of the Society of Hungarian Radiologists and 12th Annual Meeting of the European Society for Radiation Biology

To be held in Budapest, Hungary, October 19–22, 1976.

For further information please contact the Congress Office (H-1361 Budapest, PO Box 32, Hungary).

Autumn Meeting North of England Branch of B.I.R.

The autumn meeting of the North of England Branch of The British Institute of Radiology will be held at the Children's Hospital, Sheffield, on Saturday, October 30.

This is the Centenary year of the Children's Hospital and the staff will be presenting short papers. If anyone fails to receive a notice of this meeting by post would they please inform the General Secretary of the B I.R.

British Vacuum Council Prize Award

The British Vacuum Council offers a prize of £100 for a paper based on a postgraduate research thesis in vacuum or a related topic in which vacuum science and/or engineering is of major importance. The research in question must be carried out in a laboratory in the United Kingdom.

Papers submitted as entries for the British Vacuum Council prize must not previously have been published elsewhere. Entries for the 1976 prize must be submitted not later than November 1 to the address shown below, from which further details are available: The Secretary, British Vacuum Council, 47 Belgrave Square, London SW1X 8QX.

British Medical Ultrasonics Group

The Annual Meeting of the British Medical Ultrasonics Group will be held in Dundee on December 20–21, 1976.

Papers will be presented on all aspects of diagnostic ultrasound and there will be an associated commercial exhibition.

Further details from: The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiation Protection: An Example of Action Against Modern Hazards

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colegio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Book reviews

Ultrasonoscopic Differential Diagnosis in Obstetrics and Gynecology. By R. O. Meudt and M. Hinselmann, pp. 138, 1975, (Berlin Heidelberg, New York, Springer-Verlag), $40.20.

This book is essentially an illustrative atlas based on the authors' experience of more than 50,000 examinations using the Vidison real-time B scanner (Siemens Erlangen), although the single A scan illustrated (Fig. 40) is recorded with the Kretz MG 4100 (Zipf. Austria).

The aim of the atlas is to provide a practical illustrated account of the differential echoscopic diagnostic findings in obstetrics and gynaecology. This aim has been achieved only to a limited extent. The text has been restricted to a very brief explanatory introduction. None of the illustrations have an explanatory text although a number are accompanied by line drawings. The captions and introduction have been recorded in English, German, Spanish and Italian, and a useful innovation is an extending fold-out page of explanation of abbreviations at the back of the book which can be readily referred to throughout the study of the whole book.

The relatively small field covered by the Vidison Scanner greatly limits the amount of information which can be recorded on a single picture. Some of the longitudinal scans show the bladder to the right side of the picture and in others to the left and this can be rather irritating to the observer.

The first part of the atlas is concerned with the appearances in normal pregnancy at various stages and the illustrations particularly of the early stages of fetal development and of the placenta are good. Some examples of abnormal findings during pregnancy including uterus arcuatus, fibroids and also ovarian cysts are well illustrated.

Complications of pregnancy including abortion, blighted ovum, placenta praevia and abruptio placenta and hydatidiform mole are also illustrated and there are several good examples showing the features of fetal death, hydrocephalus sacral tumour, meningocoele and hydrops fetalis.

The second major section of the book is concerned with the echoscopic assessment of gynaecological tumours. This section is much less impressive and consists of a rather haphazard collection of illustrations of ovarian and other adnexal tumours and ectopic pregnancy. Some of the illustrations are rather poor and in some instances the exact nature of the mass is not indicated.

Although this work is basically an atlas, in a number of cases it is felt there is a need at least for some explanation of the differential diagnostic features shown in the various illustrations. Again the limitations of the size of the scanning field is a serious drawback in trying to demonstrate all the features of an abdominal mass. The rather poor illustrations of carcinoma of the breast and liver metastases from breast carcinoma seem rather out of place in this book.

This atlas may be of value to readers interested in appreciating the information that can be obtained in obstetrics and gynaecology using the Vidison B Scanner, and its limitations. Unfortunately this type of scanner is not widely used in this country. As a result this book is likely to create only a very limited interest in Britain, particularly as the information illustrated does not reach the very high standard of detail and quality that we have now come to expect and indeed demand from commercially available B scanners.

E. BARNETT.

Ultrasonographic Diagnosis in Obstetrics and Gynaecology. By H. Schams and J. Bretscher, pp. 193, 1975 (Berlin, Springer-Verlag), $33.60.

The layout of this book is similar to the other atlas published recently by Springer-Verlag on the same subject. The captions to the illustrations are printed in English, French, German, Spanish and Italian and once again there is a useful fold-out page of abbreviations at the back of the book. The authors state that the examples shown in the atlas have been selected from their two years of experience. The cases have been carefully checked with clinical and laboratory methods: The apparatus used is the Picker Scanner (Picker Corporation, Cleveland, Ohio).

There are 12 pages of introduction giving initially a very brief outline of the production of ultrasonic waves and the manner in which the information can be recorded, followed by a brief mention of the appearances in normal pregnancy, various complications of pregnancy, ovarian cyst, and uterine myoma. Finally there is a passing reference to the ultrasonic examination of the upper abdomen. Several misleading statements are immediately obvious in the text. For example, it is stated that the time motion or M method is a special form of the A scan, whereas it is actually derived from the B scan technique of recording. The authors also state that with the abdominal sound head, heart actions can be detected from the 13th week of gestation and that with special techniques involving the use of vaginal sound heads, or rotating directional transmitters, fetal heart actions can be detected as early as 8–10 weeks. In actual fact with a number of B scanners now commercially available fetal heart movements can be recorded routinely as early as eight weeks or less and merely listening with the Doppler apparatus the fetal heart can often be heard as early as ten weeks.

The material illustrated in the book is rather unbalanced and does not give a comprehensive cover of the conditions that may be encountered in obstetric and gynaecological practice. There is an unnecessarily large number of examples of B and A scans in bi-parietal measurement and of M mode recordings of fetal heart movements. Similar criticism can be made of the numerous illustrations of normal placenta and placenta praevia, some of which are rather poor. The section on gynaecology is largely confined to uterine myoma and ovarian masses. The small section referring to the upper abdomen is limited to cross-sectional views of the kidneys normal, hypoplastic and hydronephrotic, and two transverse scans of the liver. The illustrations in this section are poor and one gains the impression that they were included as an afterthought.

The production of an atlas such as this requires the availability of a vast amount of material, which appears to be lacking in this publication. One gains the impression that this book has been published rather prematurely. It makes little impact on the reader, and cannot be recommended as a comprehensive illustrated survey of the application of ultrasound in obstetrics and gynaecology.

E. BARNETT.

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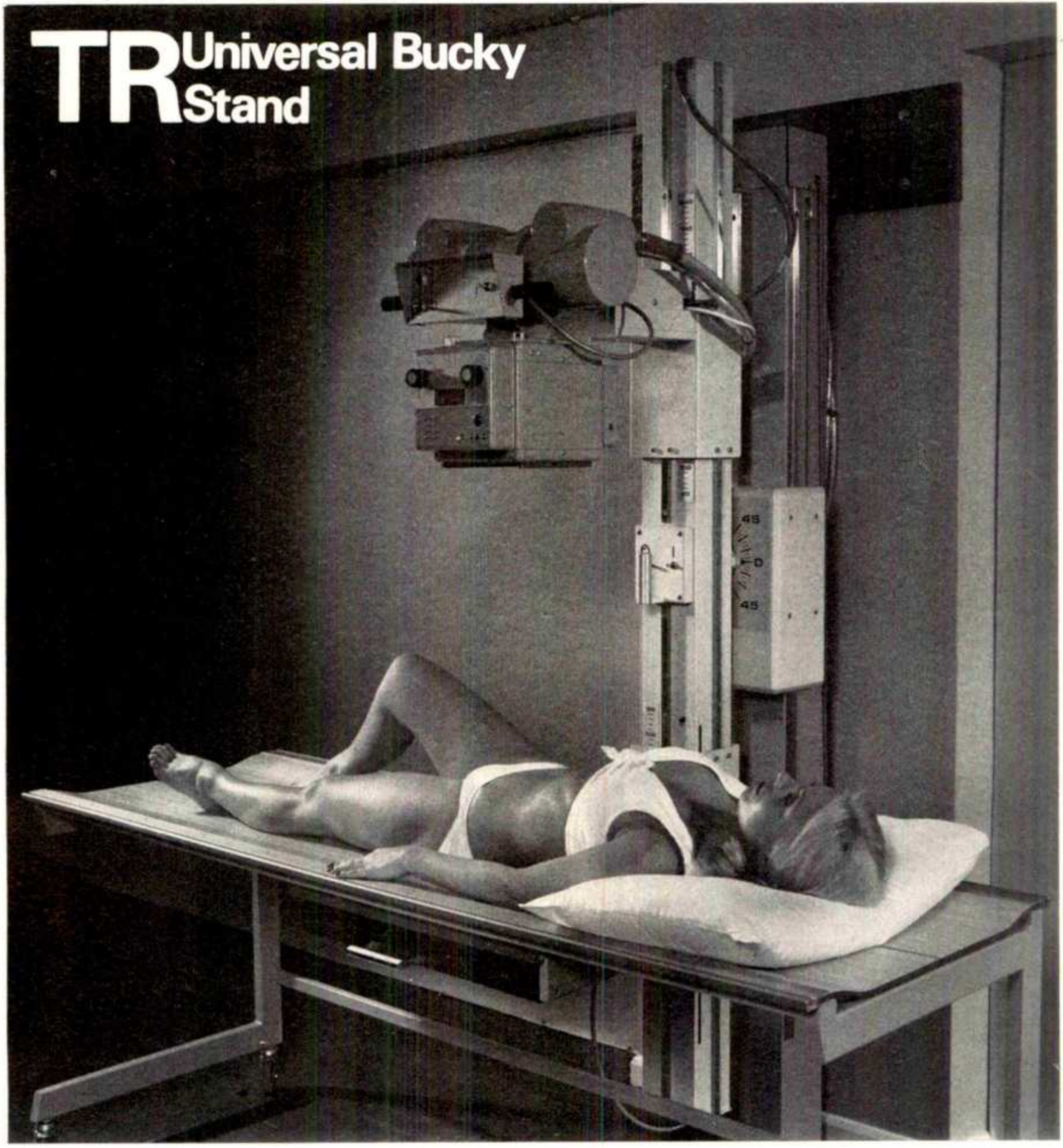

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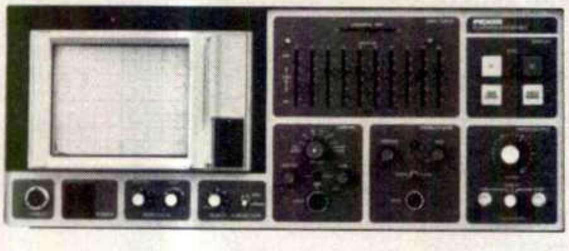

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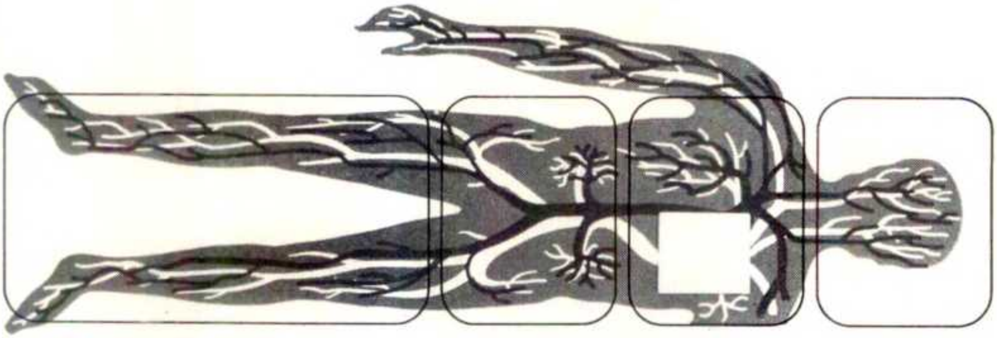

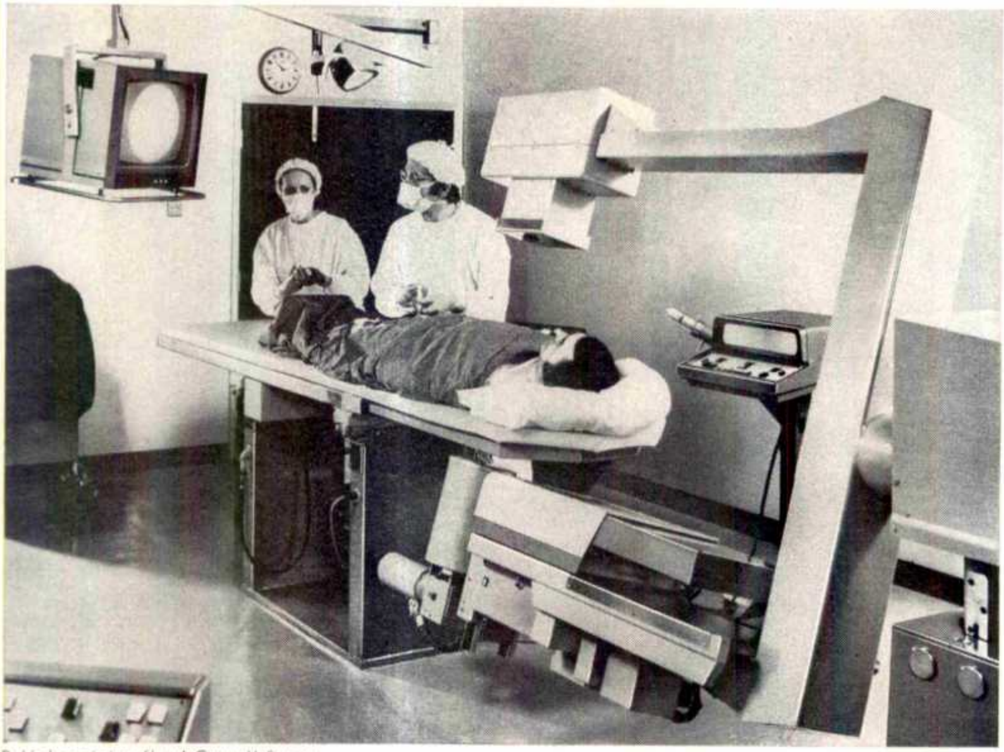

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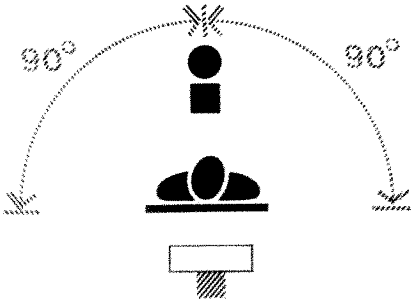

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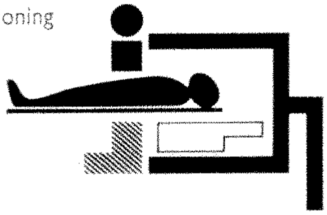

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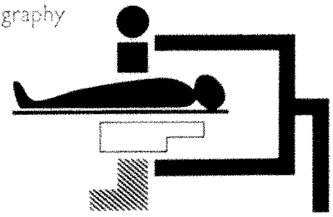

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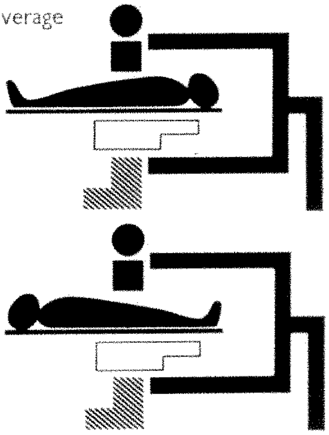

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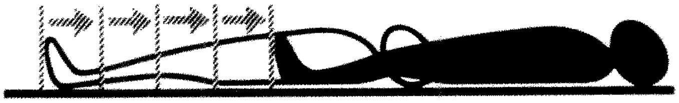

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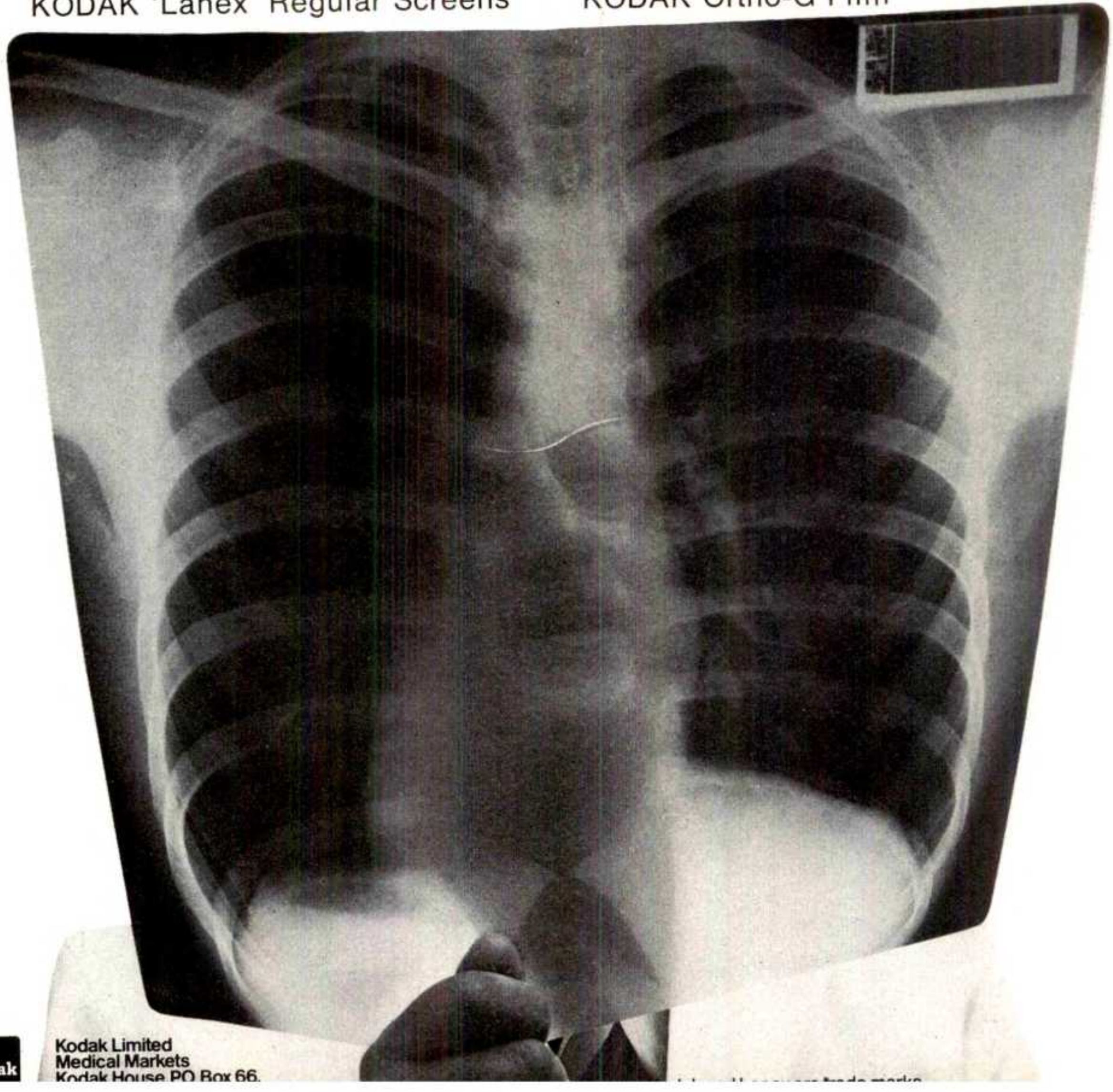

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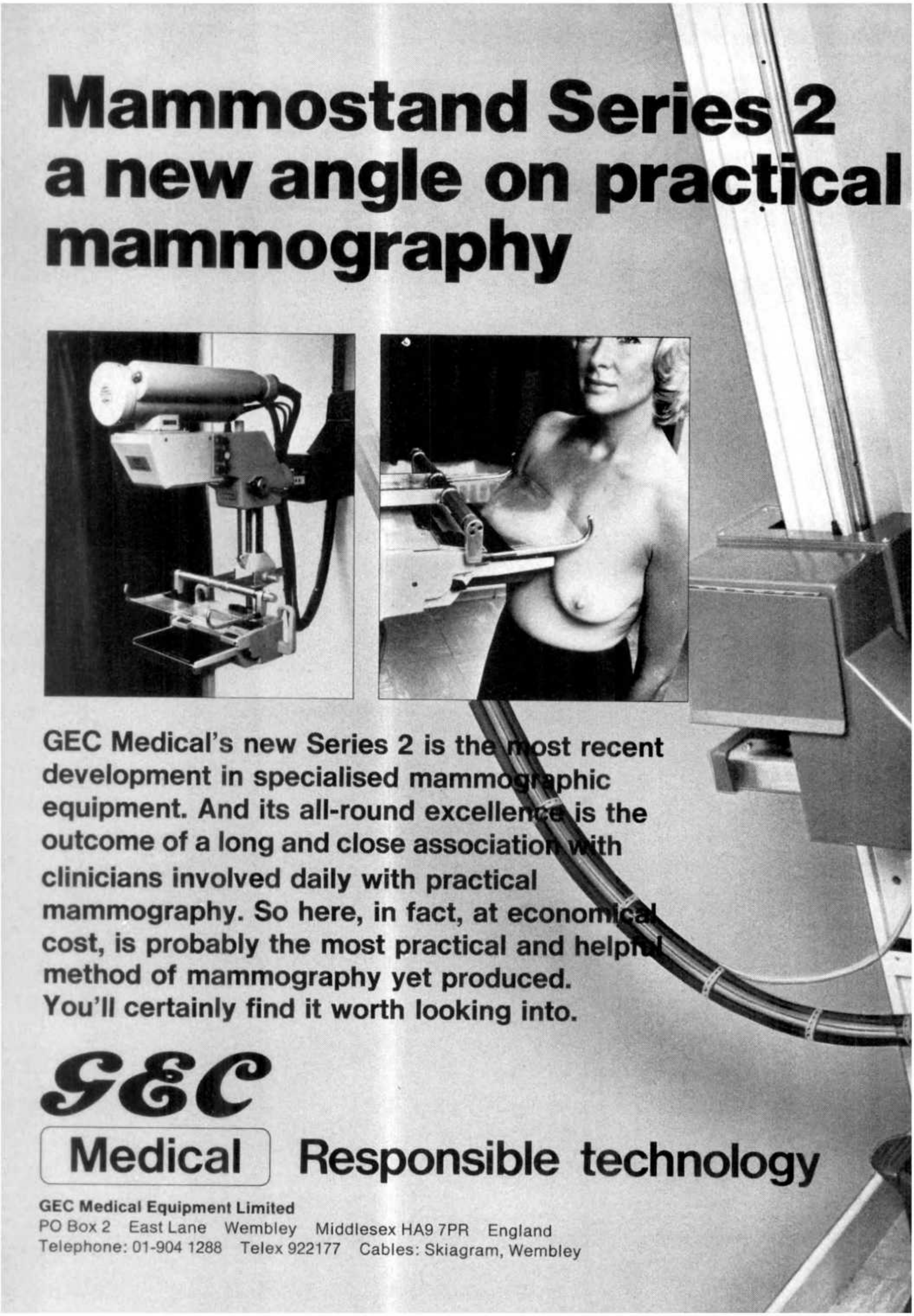

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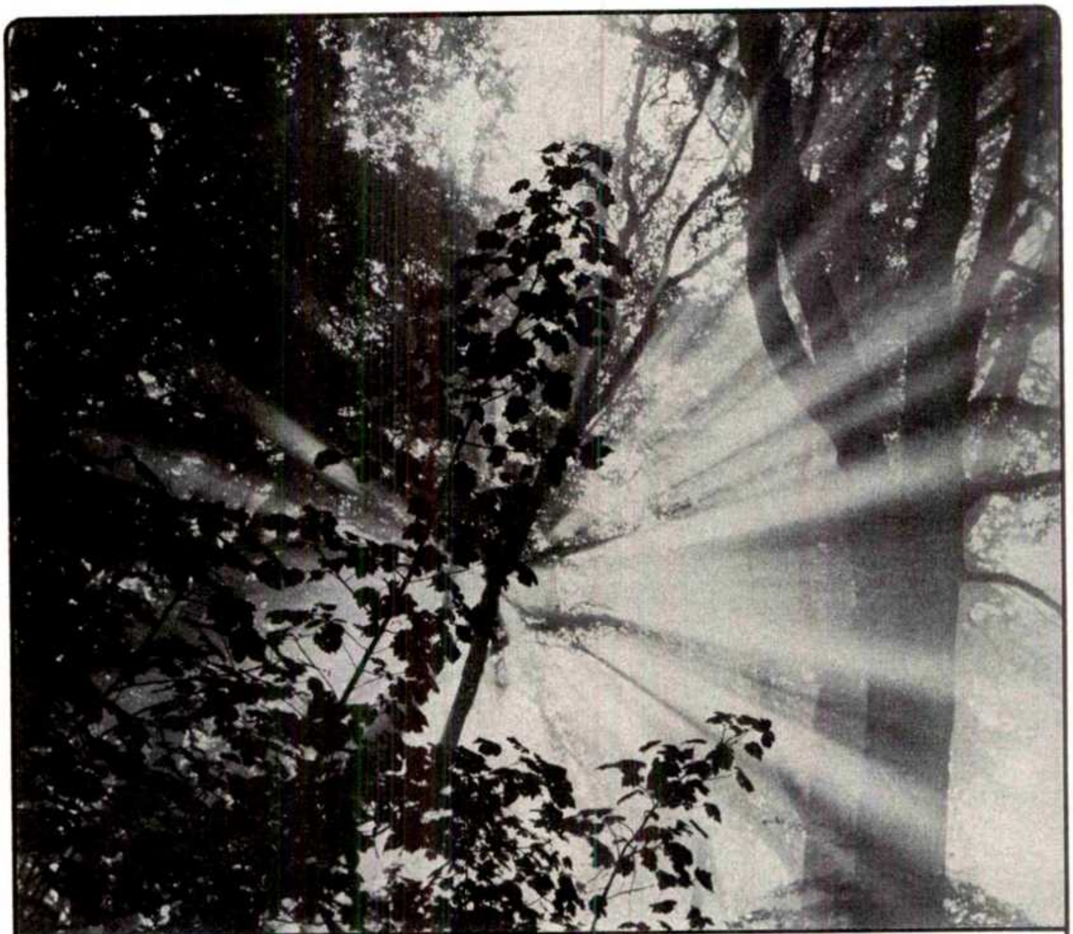

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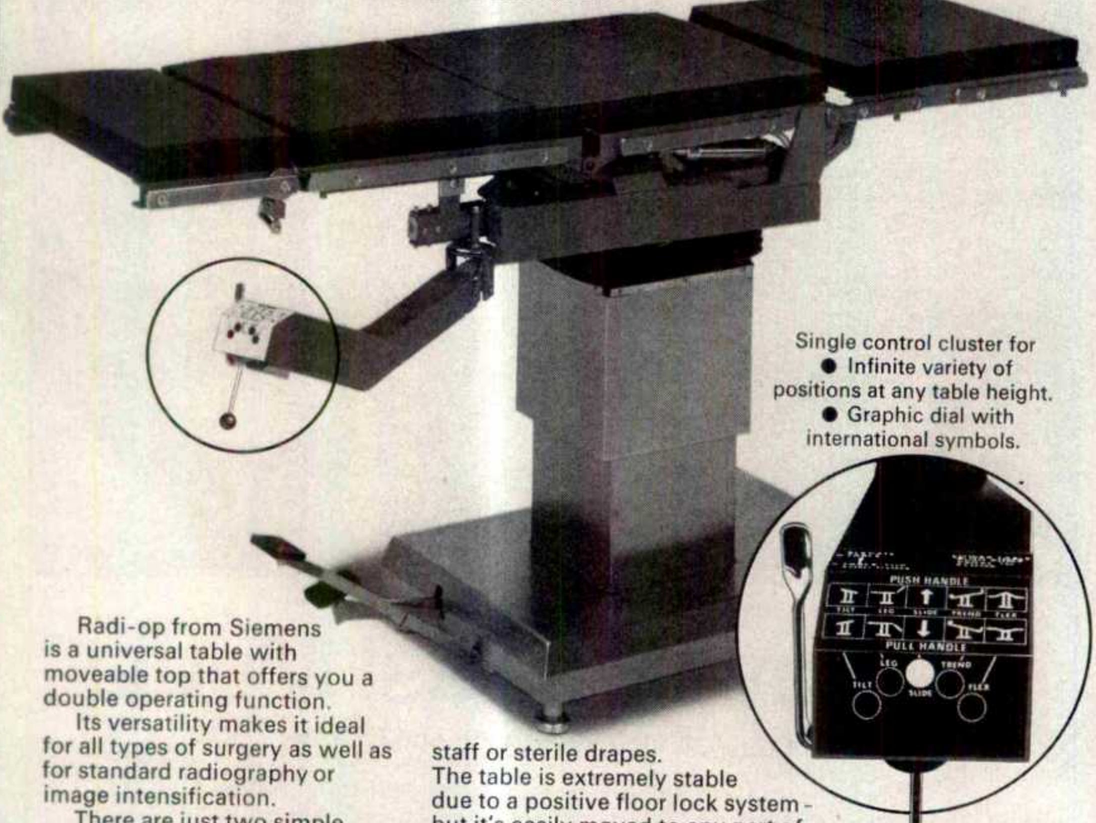

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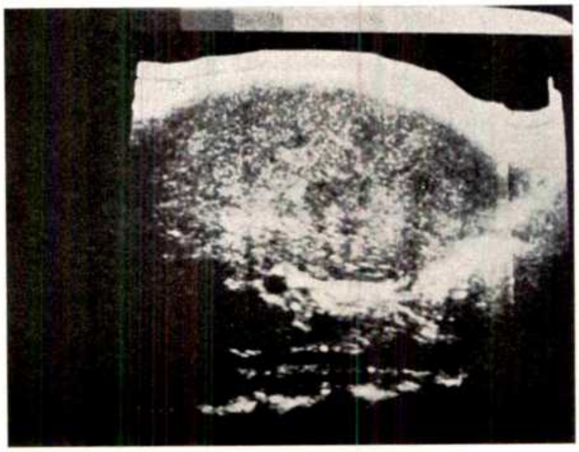

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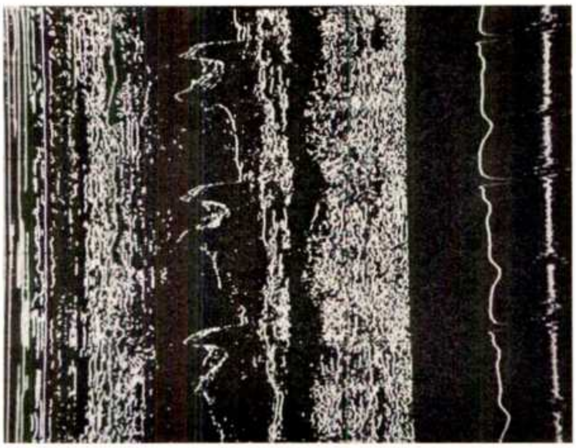

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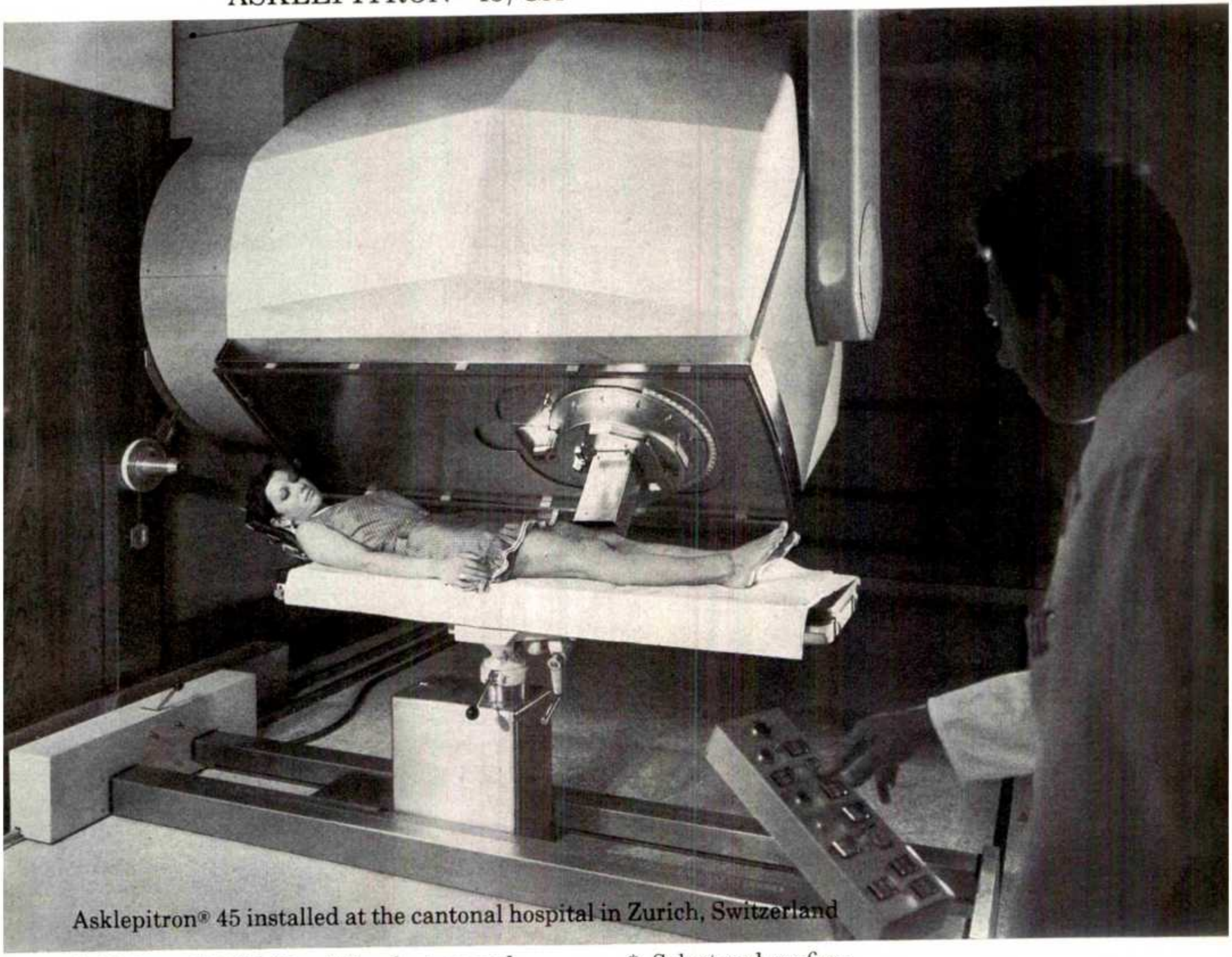

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At last, a 5MV linear accelerator that's good enough for the Philips integrated therapy programme.

The Philips Integrated Therapy Programme ensures increased efficiency in the modern radiotherapy department by having a common design philosophy, similarity of operational procedures and simplified service.

The programme embodies maximum reliability and patient safety. It incorporates a long-term plan providing the clinic and hospital with the essential equipment for today and the future.

The new Philips 5MV linear accelerator is the latest introduction to the Programme.

A machine that has been specifically designed for the radiotherapy department needing a unit for X-ray treatments when electron therapy is not required.

Fulfilling an important role.

For the smaller clinic, the SL.75/5 offers all the sophistication of the higher energy linear accelerators in the same series, but it has also been carefully designed to match other units in the 4-6MV range.

For departments where the higher energy machines are already in operation, the common design philosophy of the 5MV enables it to be readily integrated into the department.

All this makes the 5MV ideal as a primary treatment unit or a secondary unit for the larger overworked clinic.

This is what you can expect in performance.

The SL.75/5 will handle 60 patients a day.

The X-ray energy can be set in the 4-6MV range and is monitored and controlled by the same system that is used in the other Philips linear accelerators and so ensures accurate energy stability.

Dose rates at 350 rads per minute at one metre can be achieved at 5MV. (Equivalent to 550 rads per minute at 80cm.)

The maximum field size is 40x40cm at one metre F.S.D.

A 420° gantry rotation has been included to ensure rapid setting up of patient treatments.

All movements are motorised with variable speed control and have simultaneous movement capabilities.

There is also a choice of treatment tables. Either a high lift ram type or an above floor version. (A combination of table side supports and centre spine construction allows beam access from any angle.)

Safety as always.

A major aspect of the SL.75/5 design concerned safety.

The dual channel dosimetry system is backed by a timer. Select and confirm routines ensure maximum patient safety and reduce operational errors. And if required, a verification system can also be added.

Where room protection is limited, a retractable beam absorber is available that can be interlocked to prevent irradiation to unsafe directions.

Dose and time LED displays are automatically maintained in the event of an electrical supply failure.

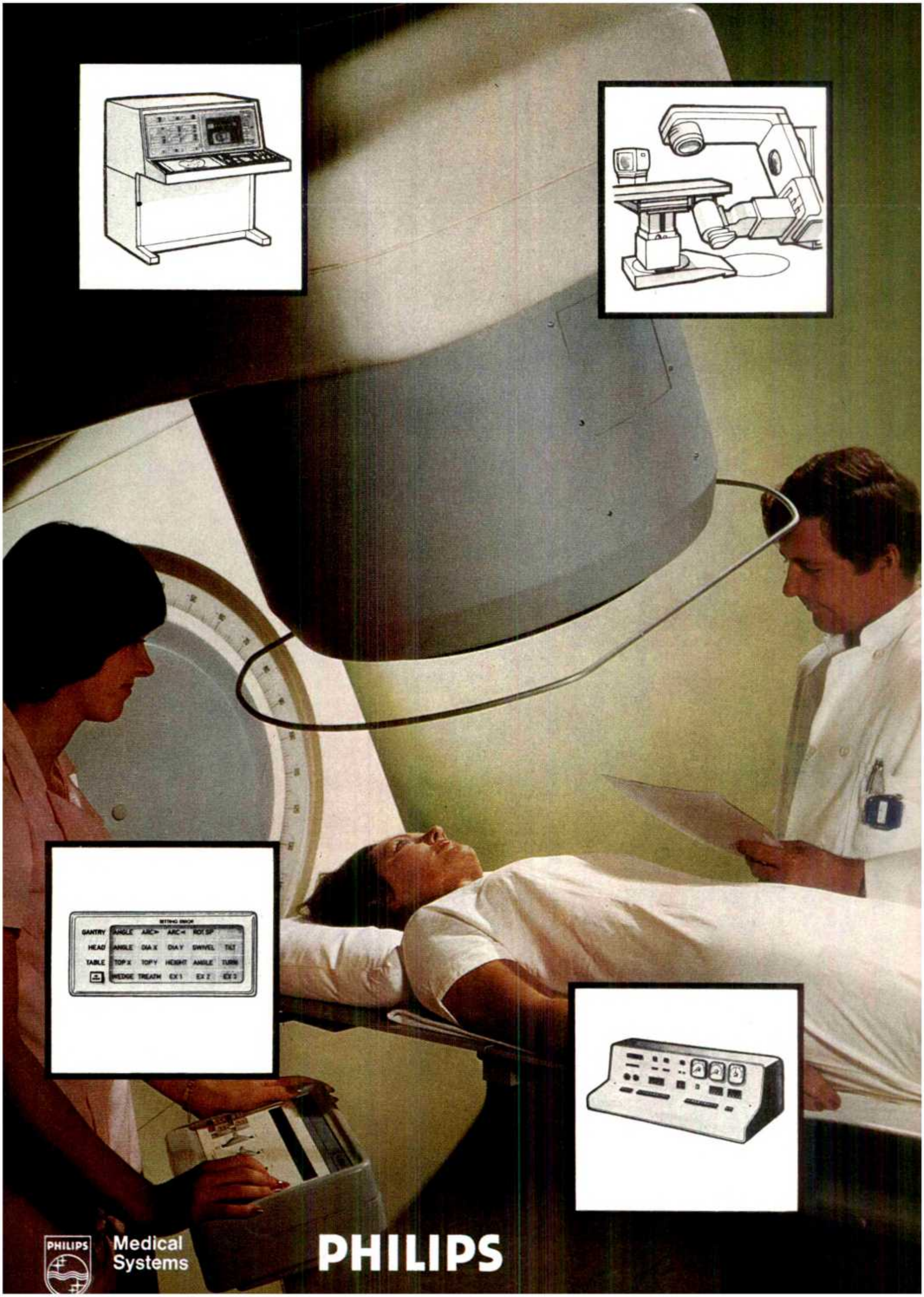
Find out more about the 5MV and the entire Philips Integrated Therapy Programme.

Here we have made a brief mention of just a few aspects that make the SL.75/5 an important addition to the Philips Integrated Therapy Programme.

The entire Programme includes cobalt units, localiser/simulator, a treatment planning system and ortho-voltage therapy units.

Philips are constantly developing new equipment for the highly specialised radiotherapy field.

If you would like to know more about the Philips Integrated Therapy Programme,
please write to: N.V. Philips, Medical Systems, Eindhoven, The Netherlands,
or The M.E.L. Equipment Company Ltd., P.A.D. Manor Royal, Crawley, Sussex, England,
or Philips Medical Systems Ltd., 45 Nightingale Lane, London SW12 8SX,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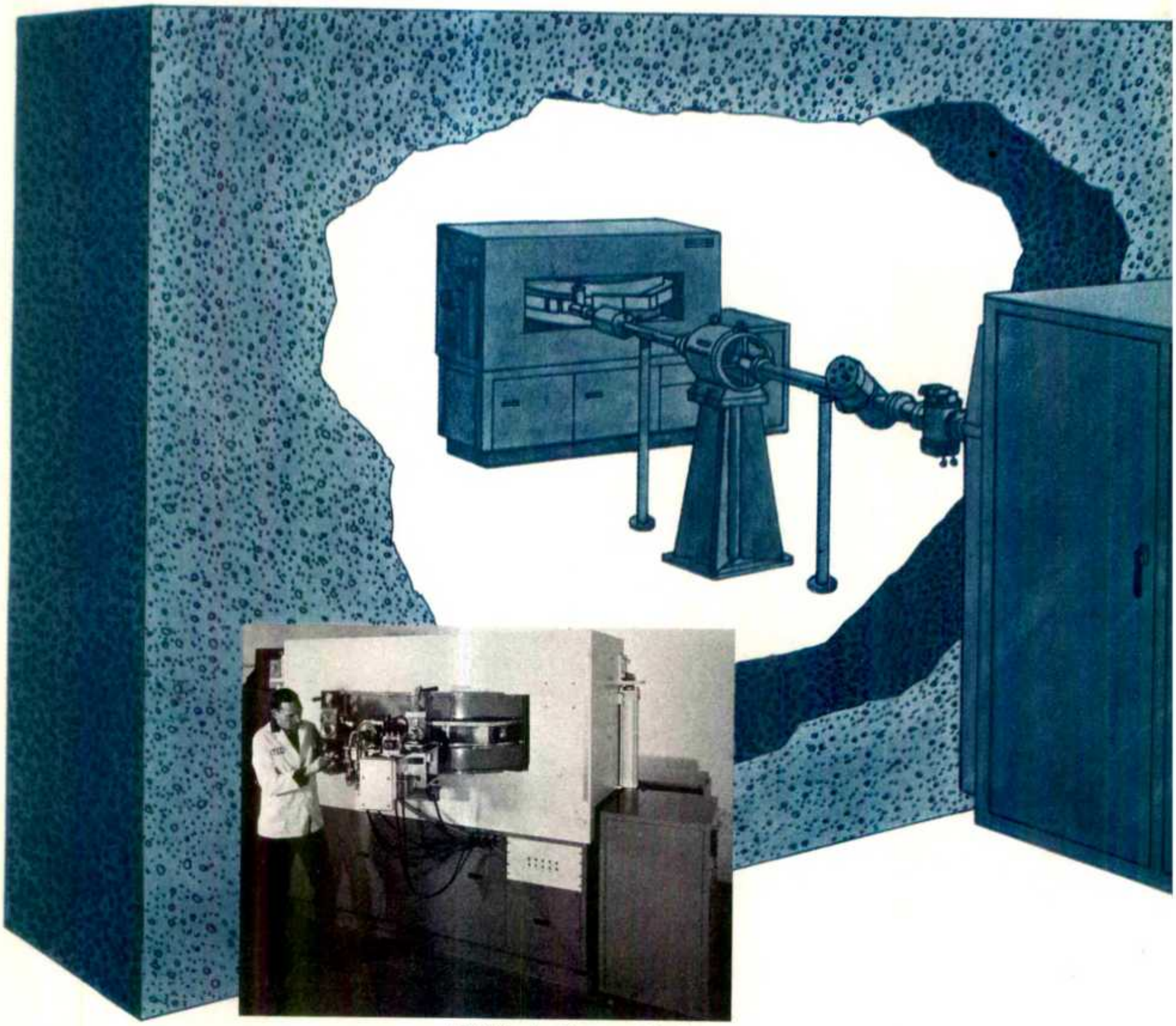


"CP" Series Compact Cyclotron

INTRODUCING a compact high performance Neutron Therapy System

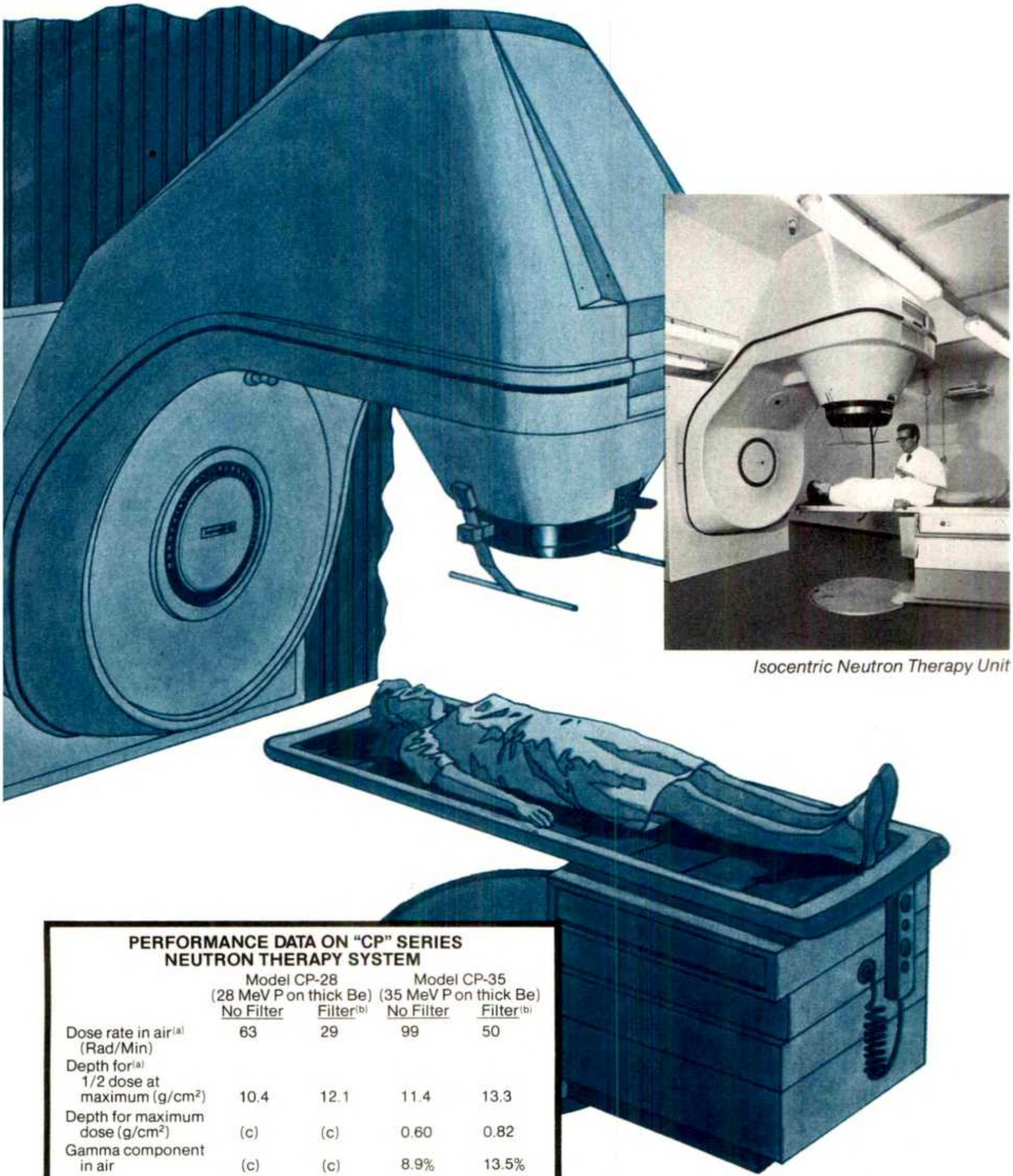
. . . incorporating a cyclotron and isocentric therapy unit. The compact cyclotron design is based on more than twenty machines of its type built by The Cyclotron Corporation which are currently in use all over the world. These machines have proved to be very reliable —several are operated routinely over 100 hours per week.

The isocentric neutron therapy unit has been tested successfully in the factory. One is now being installed at Western General Hospital, Edinburgh, Scotland, and another at Universitätsklinikum, Essen, West Germany.

Two models of this new "CP" Series therapy system are currently available, and the performance of each is summarized in the adjoining table.

Production of fast neutrons via the proton on beryllium reaction makes possible high performance with a relatively small accelerator and isocentric therapy unit. Such a system including shielding can be installed in an area of 13m (43 ft.) by 20m (66 ft.). Vertical height required with shielding is 5.5m (18 ft.).

The price of the "CP" Series system is generally comparable with the selling price of high energy accelerators for electron and photon therapy.



Isocentric Neutron Therapy Unit

PERFORMANCE DATA ON "CP" SERIES NEUTRON THERAPY SYSTEM

	Model CP-28 (28 MeV P on thick Be)		Model CP-35 (35 MeV P on thick Be)	
	No Filter	Filter[b]	No Filter	Filter[b]
Dose rate in air[a] (Rad/Min)	63	29	99	50
Depth for[a] 1/2 dose at maximum (g/cm^2)	10.4	12.1	11.4	13.3
Depth for maximum dose (g/cm^2)	(c)	(c)	0.60	0.82
Gamma component in air	(c)	(c)	8.9%	13.5%

Note

(a) $n + \gamma$, 10 cm. x 10 cm. field at 125 cm. SSD
(b) Filter is 6 cm. polyethylene
(c) Not measured

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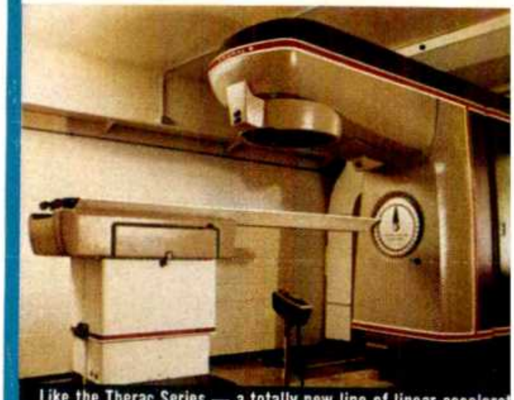
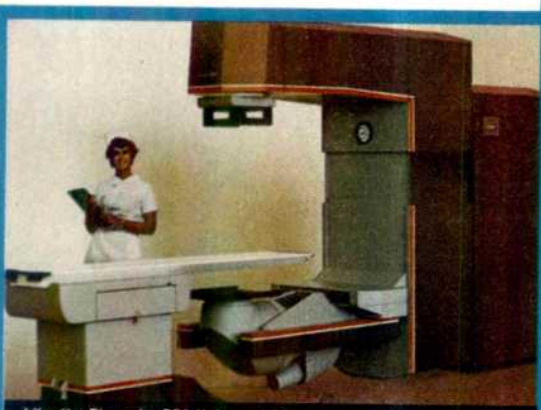
— But there is MUCH MORE!



Like the Therac Series — a totally new line of linear accelerat
with energy output from 6 to 40 MeV.



Like the Therasim 750 Universal Simulator — AECL pioneered the design of therapy simulators for use with all makes of accelerators, betatrons and Cobalt 60 units.

Like the T.P. 11 treatment planning system — a sophisticated bl
of computerization and electronics which adds a new dimens
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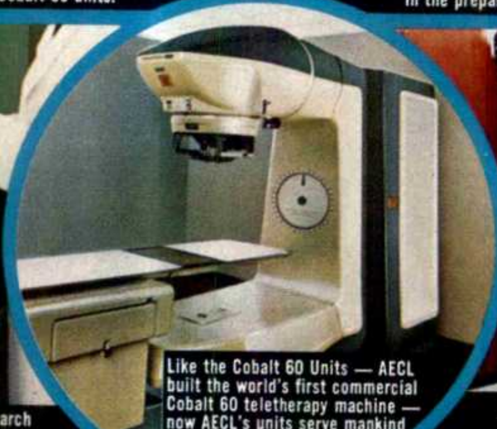
Like the Gammacell 40 Biological Research Irradiator — Hundreds of AECL research irradiators are in daily use around the world.



Like the Cobalt 60 Units — AECL built the world's first commercial Cobalt 60 teletherapy machine — now AECL's units serve mankind in over 70 countries.

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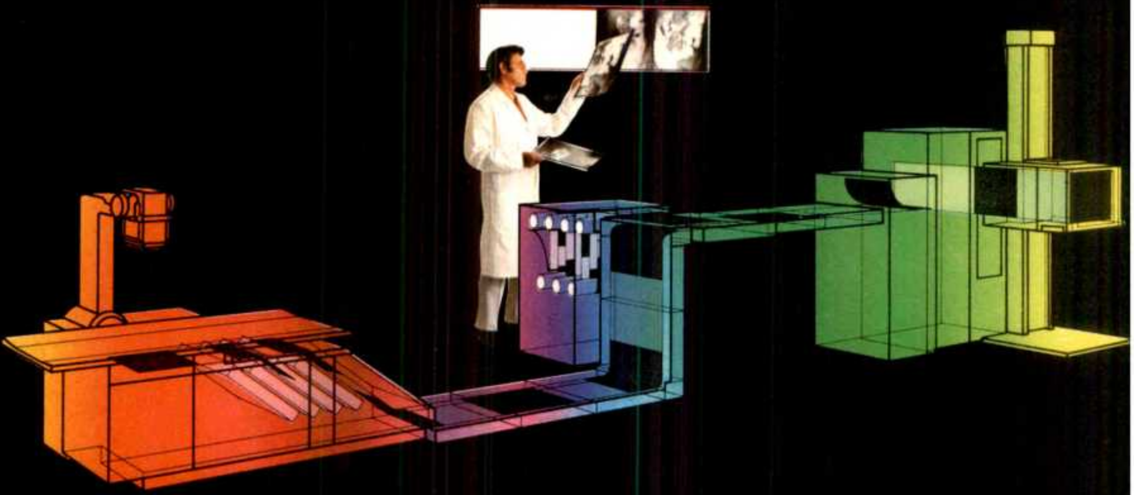

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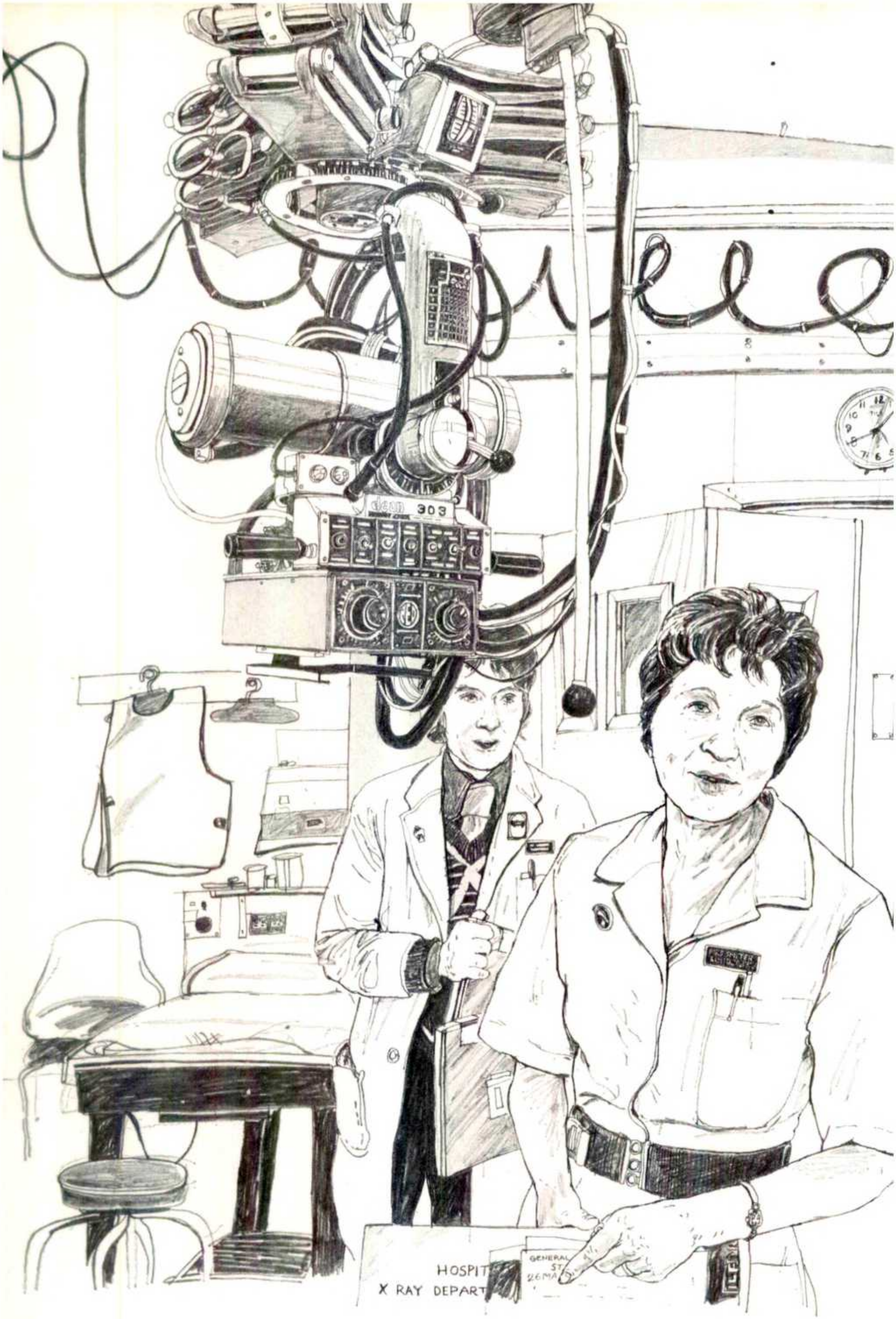
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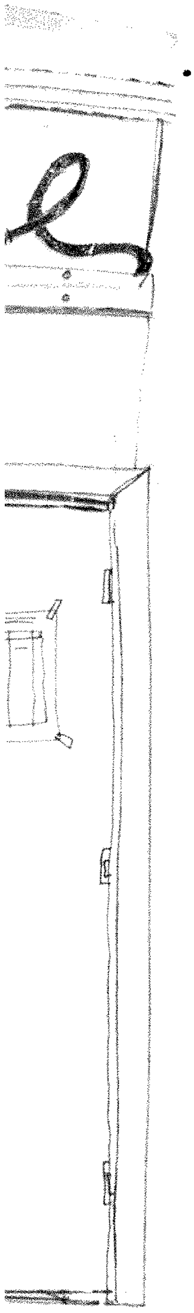

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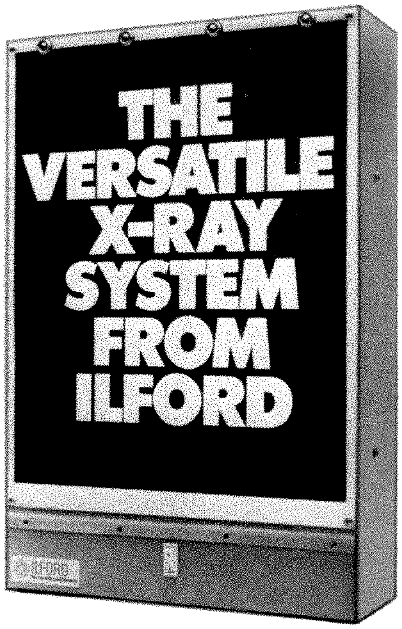

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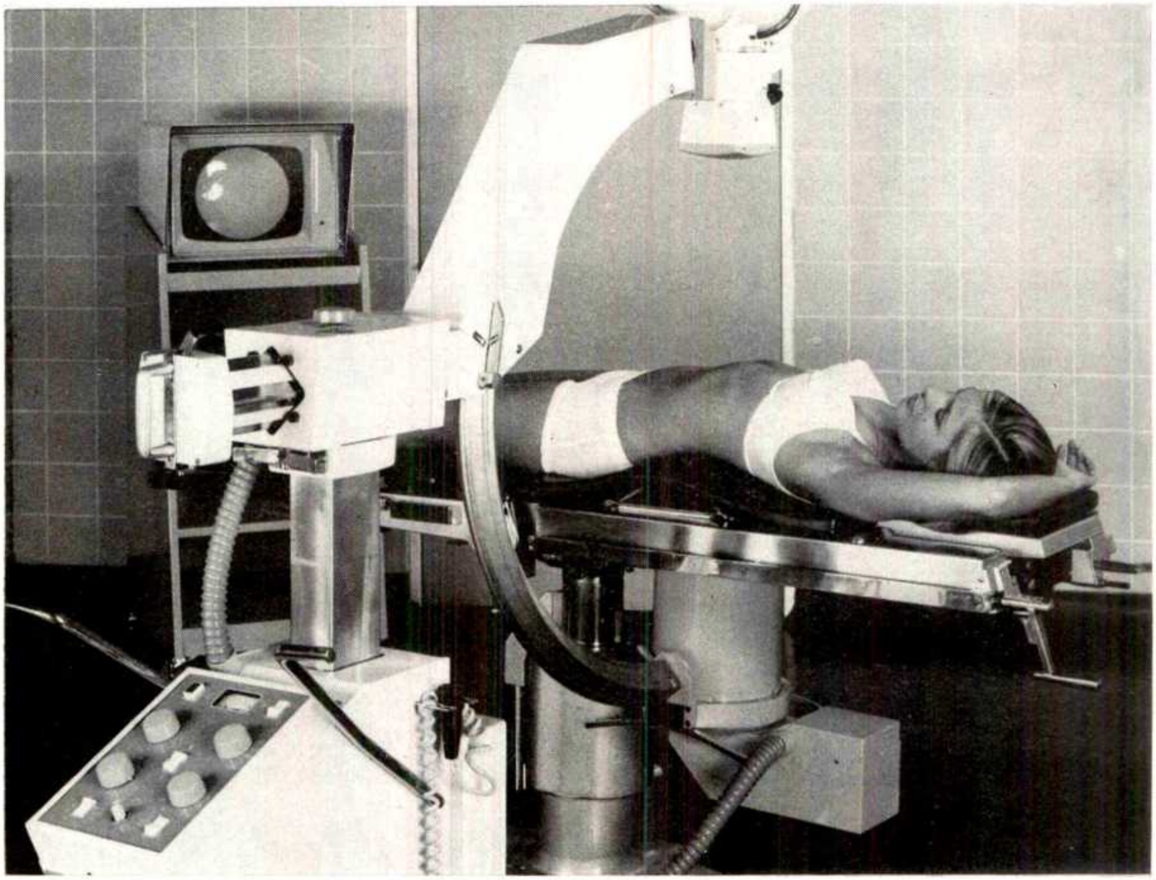

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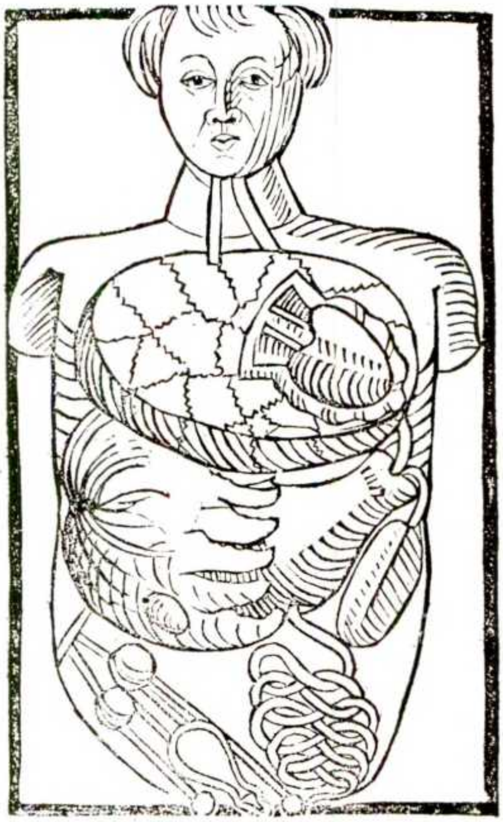

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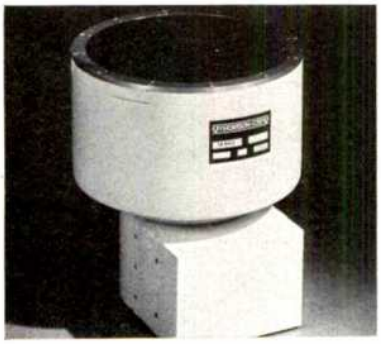

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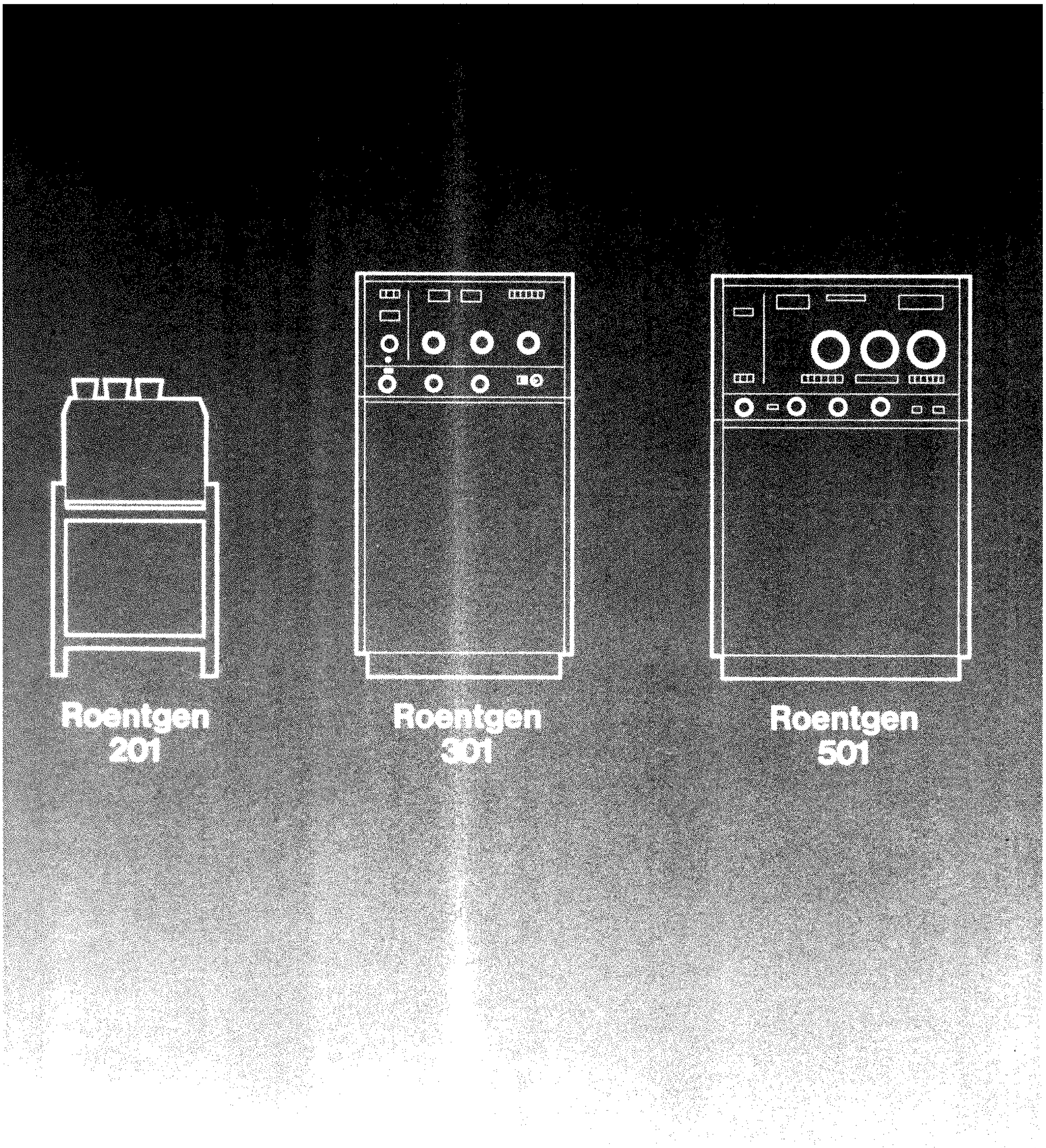
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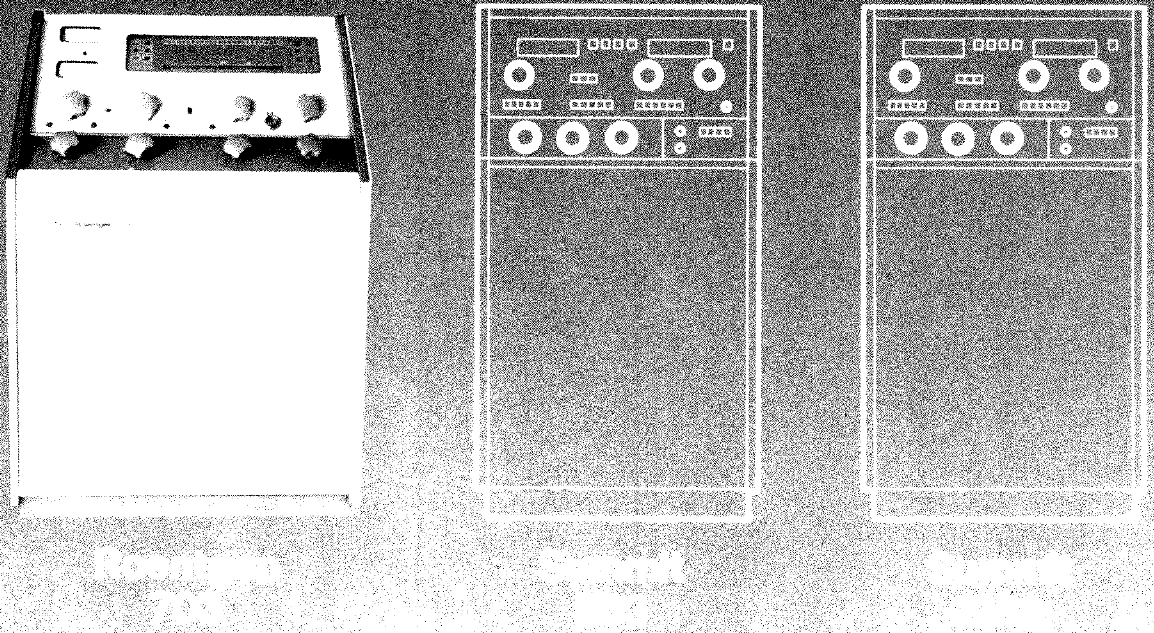

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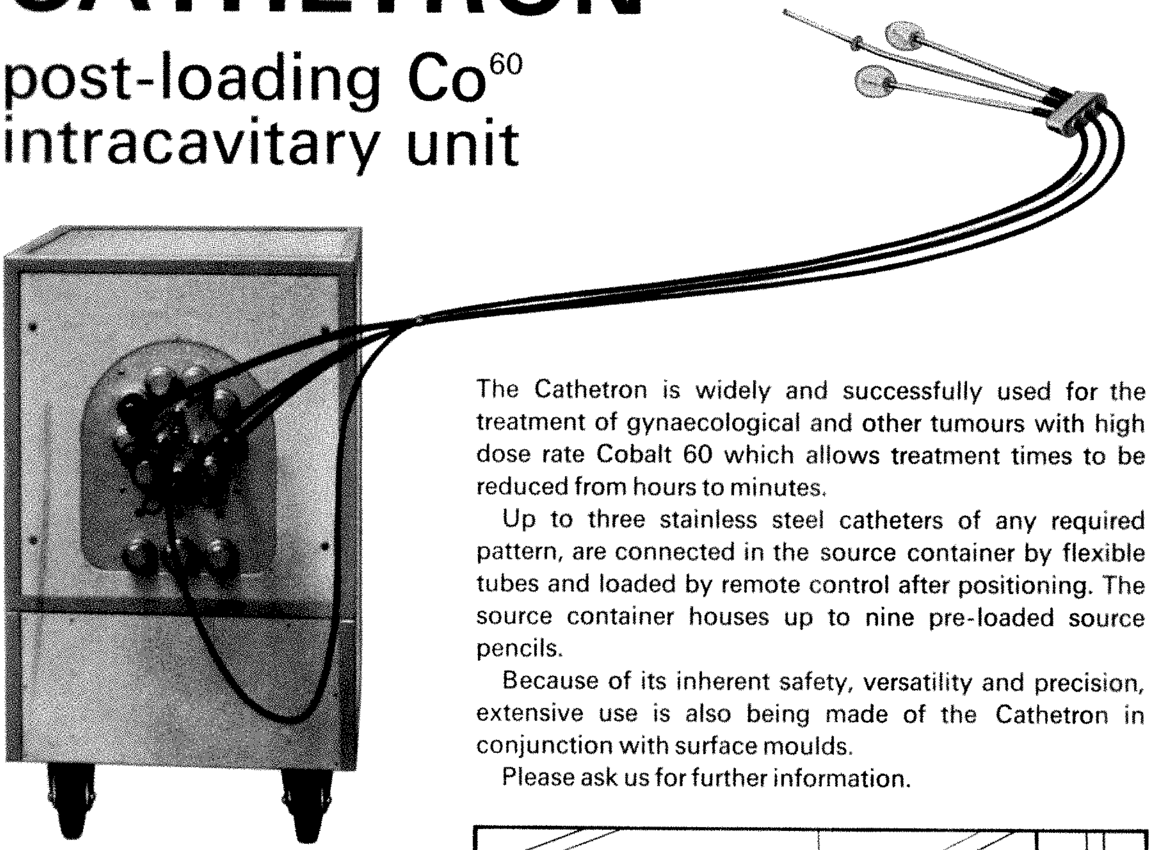

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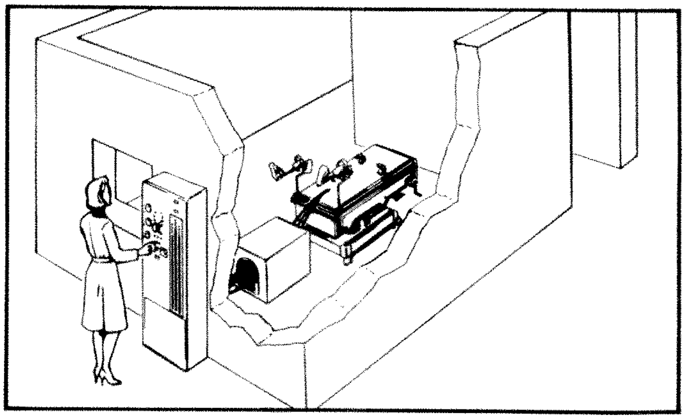

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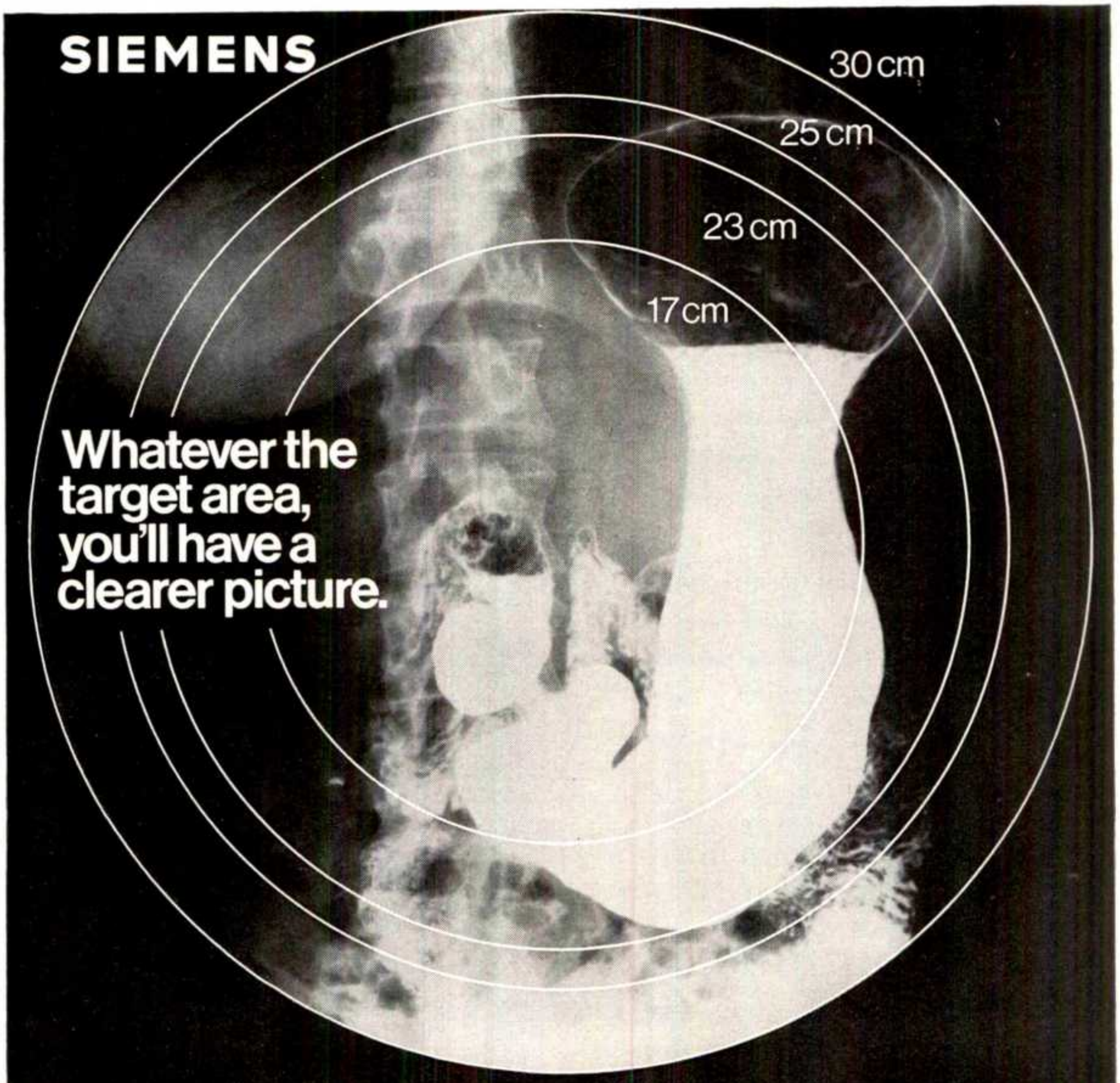

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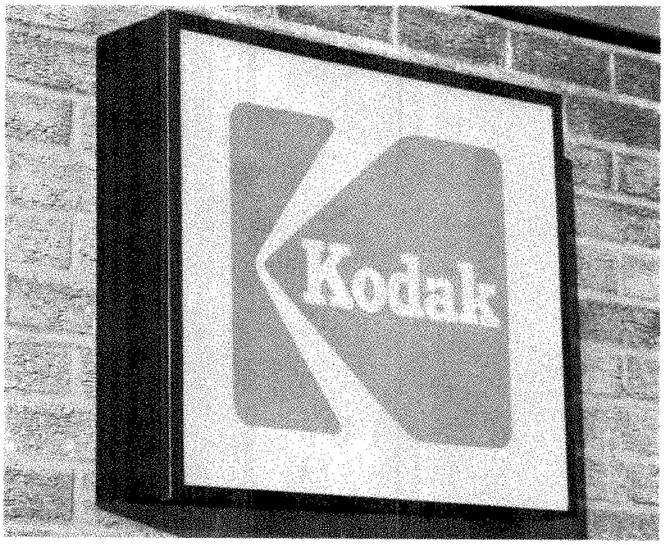

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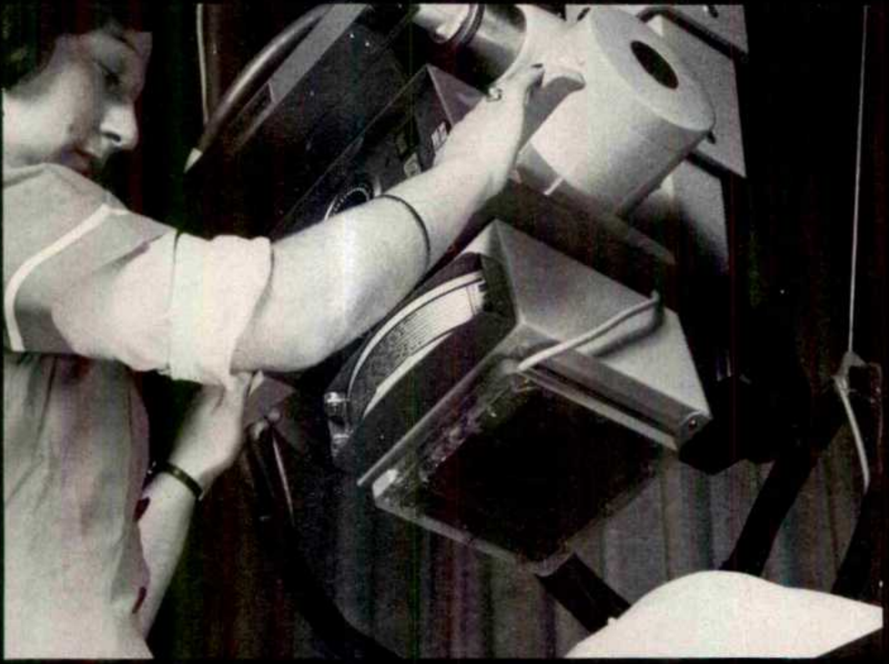

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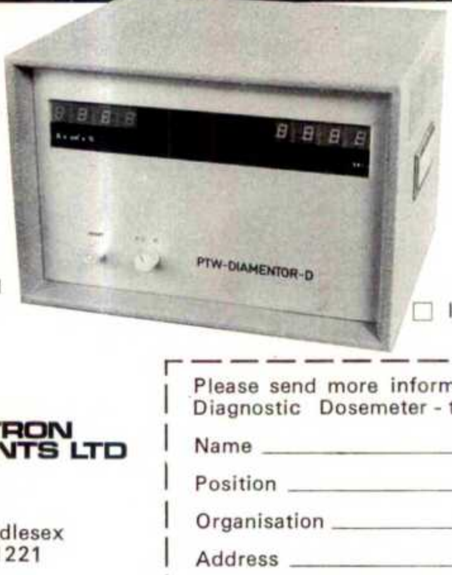

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We are pleased to announce the publication of this report on treatment simulators. The report discusses the uses of simulators in radiotherapy and sets out guide-lines for their future development, both in the specifications of design parameters and in techniques for use. The specifications of simulators currently available from a number of manufacturers are tabulated and compared with those considered desirable by the authors.

The authors point out that the simulator has been a radiotherapy aid for a quarter of a century, but that to many its purpose and use are still undefined ; they take the view that although verification is an important function of a treatment simulator, its main function is the accurate localization of the tissues in the region to be treated.

This Report is one of several now in preparation under the general title *Applications of Modern Technology in Radiotherapy.* The authors were brought together as a working group following discussions between members of The British Institute of Radiology, the former Faculty of Radiologists, the Hospital Physicists Association and The Society of Radiographers on the general need for information and guidance on the most effective ways of bringing new advances in technology into wide use in radiotherapy. We believe that this first report will prove of considerable interest to many present and prospective users of treatment simulators in Great Britain and in many other countries.

Members of the working group :
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The British Journal of Radiology

Radiology now

Renal trauma: the place of arteriography*

In an era of super-mechanization and of an insatiable desire for moving fast, there has been a notable increase in the number of patients suffering multiple system injuries. Although the kidney is mobile and relatively well protected by its position in the body, the violence of modern trauma takes its toll with injuries varying from mild contusion to laceration and, in severe cases, to shattering of renal substance and major renal vessel damage.

The diagnosis and treatment of renal injuries is one of the most controversial topics in urology. The spectrum of management is from aggressive surgery to watchful waiting, but never, one trusts, masterful inactivity. Renal injuries rarely threaten a patient's life. Clinical and radiological management is dependent upon careful and complete diagnosis of the injuries. The radiological techniques now available allow accurate assessment of the anatomical lesion, resulting in a significant improvement in morbidity and preservation of functional renal tissue. There are hawks and doves in the management of renal trauma as there are in other aspects of life: the more aggressive approach with immediate angiography and surgical exploration (Halpern, 1968; Villar *et al.*, 1972), or the conservative approach which is successful in the majority of patients (Slade, 1971).

Two recent papers might again stimulate discussion about whether and when arteriography should be performed in patients with renal trauma. Cockett *et al.* (1975) declare that renal arteriography and renal scintigraphy (^{197}Hg or ^{131}I hippuren) are the diagnostic procedures of choice and claim that these investigations yield the most information. Pryor and Williams (1975) are the doves in our discussion. They use intravenous urography as the investigation of choice and reserve arteriography for clinical and radiological indications which are clearly defined. The opposing views on the use of arteriography in renal trauma can be expressed more defiantly. Halpern (1968) stated "Renal angiography in cases of acute renal trauma provides a precise anatomic assessment of the integrity of the renal parenchyma and renal vasculature, which is paramount to the ultimate fate of the kidney". Korobkin and Binder (personal communication) state the opposing view: "The more precise evaluation of renal injury possible with renal angiography just does not justify its routine use, since neither treatment nor prognosis is usually altered by this information."

It is the role of the clinical radiologist to guide clinician colleagues in the radiological care of a patient with renal injuries. The radiological management is dictated by the clinical information presented and the radiological facilities and expertise available. Plain radiography is of limited value, but intravenous urography using a high dose of contrast medium, e.g. about 800 mg iodine per kg., as in 2 ml. of Conray 420 per kg bodyweight, with tomography, is essential as the initial investigation. It should be done at the earliest opportunity to establish a baseline for further clinical care and radiological investigation. A second kidney must be proved to be present and normal, and underlying renal disease, *e.g.* hydronephrosis, cystic disease, tumour, etc. excluded.

It should be remembered that approximately 85 per cent of all renal injuries go on to complete recovery without residual deformity and nephrectomy is performed infrequently—probably in less than 3 per cent of cases. Studies of the incidence and types of renal damage show that patients with renal injuries fall into three groups. 60–65 per cent of injuries are regarded as minor, presenting with mild to moderate haematuria. The clinical state remains stable and the intravenous urogram is normal. In the second or major injury group (30–35 per cent), patients have severe or persisting haematuria, possibly a renal mass, unstable clinical signs and extravasation of contrast medium on intravenous urography, either intrarenal or extrarenal. 1–5 per cent of patients fall into the third group; catastrophic renal injuries. There is immediate and sustained shock with or without haematuria, a falling haematocrit, and intravenous urography may reveal non-function of a kidney or gross distortion of renal architecture, with extravasation of contrast medium.

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*Reprints from Dr. J. E. Williams, Department of Diagnostic Radiology, St George's Hospital, Blackshaw Road, London S.W.17.

Such a description of the incidence and types of renal damage indicate quite clearly that renal arteriography rarely need be performed as an emergency investigation. The intravenous urogram is the investigation of choice in an emergency. The surgeon who wishes to perform an emergency laparotomy in renal trauma should be persuaded that the patient be investigated by intravenous urography on the way to the operating theatre. The removal of a single kidney, or the partner of a kidney damaged previously by some other condition, is a tragedy. If the intravenous urogram reveals non-function of a kidney or gross distortion or rupture, then arteriography is indicated as an immediate investigation. Other indications for renal arteriography may be termed intermediate and late. Intermediate indications are clinical deterioration, recurrence of abnormal physical signs, including delayed haematuria and the presence of a murmur heard over the renal area, indicating an arterio-venous shunt. The late indication, which is uncommon is, the development of hypertension. It may be the result of major renal artery narrowing, the "Goldblatt" kidney, or due to a constricting capsular lesion, that is a subcapsular haematoma, the "Page" kidney (Marshall and Castellino, 1971).

What renal arteriography does demonstrate is viability of renal parenchyma which may be in doubt or jeopardy in a small number of patients. If the nephrographic phase of the arteriogram shows homogeneous perfusion of renal substance, the kidney is viable. A mottled or absent nephrogram indicates infarction in part or whole of the kidney. It is also important to state that renal arteriography may be essential for the conservative management of severe cases, when the intravenous urogram is non-contributory or equivocal.

Review of the literature and experience teach there is clearly a place for renal arteriography in the investigation of a patient with renal trauma. However, its use is limited and dictated by the combined indications of the patient's clinical condition and the results of high-quality intravenous urography.

J. E. WILLIAMS.

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Book review

Cancer of the Head and Neck. Edited by R. G. Chambers, A. M. P. Jansen de Limpens, D. A. Jacques and R. T. Routledge, pp. 366, 1975. (Amsterdam and Oxford, Excerpta Medica; New York, American Elsevier Publishing Co. Inc.), $53.95.

This publication in English is of the proceedings of an international symposium on cancer of the head and neck, held in Montreaux in April 1975.

In the first section there are papers on the combined therapy approach which is now receiving renewed attention as individual techniques improve, reach their limits and new hopes are raised by joint efforts in patient management. There are accounts of the basic principles of chemotherapy as applied to head and neck cancer and its possible role in combination treatment. There is an excellent paper on malignant tumours of the middle ear and mastoid treated in the Royal Marsden Hospital.

Surgical management includes that of skin cancers around the orbital region, malignant melanoma, the buccal mucosa, palate, floor of mouth and tongue. There are papers on tonsillar, oropharyngeal, laryngeal and laryngopharyngeal cancer treated by surgery. There are excellent review papers on malignant tumours of the nasopharynx and carcinoma of the sinuses.

One particularly interesting account concerns dental aspects of head and neck malignancy and the management of these problems. There are many well illustrated and informative accounts of reconstructive surgery. This book emphasizes the need for the closest liaison between clinicians in different fields who handle malignant disease. It is a publication which is perhaps of greatest value to the experienced clinician who wishes to know a little more about the possibilities of other modalities of treatment.

B. T. HALE.

1976, *British Journal of Radiology*, *49*, 745–764 SEPTEMBER 1976

New methods of imaging in diagnostic radiology*

Sylvanus Thompson Memorial Lecture given on October 9, 1975 at the Royal Institution, Albemarle Street, London, W.1.

By H. E. Johns, B.A., M.A., Ph.D., LL.D., D.Sc., F.R.S.C.
Physics Division, Ontario Cancer Institute, University of Toronto, Canada

(*Received January 1976*)

ABSTRACT

A brief history of the recent developments in computer-assisted tomography (CAT) is presented. The development of whole-body scanners from the basic brain scanner, the trend towards higher-speed scanners using multiple detectors in a fan-type geometry, and some of the unsolved problems related to CAT scanners are discussed, as well as the potential use of whole-body scanning in radiotherapy treatment planning and in radiobiology. A review of recent developments in electrostatic imaging is presented and a new method of imaging called ionography is described in detail. It is shown how a single exposure can be used to produce a number of copies, each with a different amount of edge contrast, under the control of the radiologist. Further, it is shown how this can be done using a closed system so that the ionography chamber never needs to be opened. Some of the recent commercial developments in this field are described. It is suggested that in the future radiology departments may be replaced by departments of imaging, which will include all ways of obtaining diagnostic information and where such a department would be problem oriented rather than technique oriented. The need for basic scientific support by a medical physics and engineering group in such a department is emphasized.

I am indeed honoured to be given the opportunity of presenting the Sylvanus P. Thompson Memorial Lecture—all the more so when I realize that I am the 54th lecturer—following after such illustrious scientists as Rutherford, Bragg, de Broglie and J. J. Thomson—men who stand at the very corner-stone of modern physics—and, more recently, after men such as Mayneord and Gray—who laid the foundation of our present concept of medical physics.

As well as being an outstanding physicist, our first president, Sylvanus Thompson, was a mathematician and an engineer. It so happens that tonight I am speaking on a subject which has been made possible through the active collaboration of physicists, mathematicians and engineers.

In the past 30 years there have been major advances in the treatment of tumours through the introduction of high-energy machines such as cobalt-60 units, betatrons and linear accelerators. In spite of the efforts of physicists working with radiotherapists, the cancer problem has not disappeared.

For a few years following the discovery by Watson and Crick of the DNA helix, there was great excitement in biological circles that this major break-through in biology would bring with it a solution to the cancer problem. It was because of this hope that many physicists, including myself, entered and spent a few years in the field of molecular biology. To illustrate the pressure for such a move I am reminded of an event which occurred some 15 years ago when I received a telegram from one of my associates who was attending a cancer conference in Atlantic City. It read, "Sell betatron, sell cobalt unit, convert all available space to animal quarters, cure for cancer will come from polyoma virus research. Will be home tomorrow to discuss details." I have now returned to physics and radiology because I am convinced the solution to the cancer problem at the fundamental level is a long way off, and because I feel we must again push the sciences of diagnostic and therapeutic radiology as far as possible towards an interim solution.

One of the main problems which still has not been solved is the localization and visualization of tumours while they are small enough to be cured, and before they have had time to metastasize. I believe that not much more progress can be made in cancer treatment until better methods are found to determine the position and extent of the tumour.

In the past few years remarkable advances have been made in fields related to diagnostic radiology, and it is about this subject that I would like to speak tonight. I became interested in this field of research through my association with Professor J. W. Boag, during my sabbatical leave which I spent in his laboratory during in the winter of 1971/72.

During that six-month period, Dr. Boag and I found a new method of imaging called ionography, which I will discuss later. At the same time, another development came on the scene. I refer to computer-assisted tomography (CAT). Interest in this field was generated on the North American continent at a meeting of the Radiological Society of North America in December 1972, where the brain scanner invented by Hounsfield, and produced by the EMI Company, was discussed by Ambrose (1973). A year later, it was exhibited at the next meeting with very great interest. The following year (December, 1974) the most exciting topic of conversation was related to recent developments and possible improvements to the EMI-scanner. Two conferences were held in the spring of 1975 in Bermuda and in Puerto Rico, both of them dealing with developments in scanners.

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*Copies of this Memorial Lecture may be obtained from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG at a cost of 75p; remittance with order please.

First, I will try to summarize the field of scanners, indicate some of the interesting problems which have not yet been solved, and attempt to speak of the future of such devices. Next, I will discuss xeroradiography, and a natural outgrowth of this—ionography.

COMPUTER-ASSISTED TOMOGRAPHY

Now what is computer assisted tomography? In a conventional radiological tomograph the source of X rays and the film are moved during the exposure in such a way that only the one plane containing the area of interest is kept in focus and the other planes are blurred out. However, the picture is usually not sharp because the tissues above and below the plane of interest, although out of focus, are also projected and recorded on the film as noise. Computer-assisted tomography is quite different. The principle is illustrated in Fig. 1. A pencil beam of X rays passes through the tissue plane of interest and is measured by a small detector. The detector and X-ray tube are moved along parallel lines so they bear a fixed relationship with respect to each other, yielding the

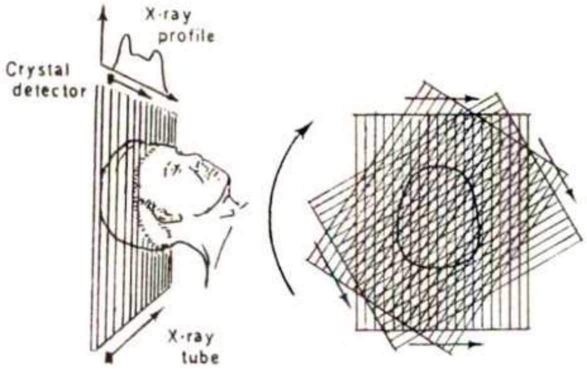

FIG. 1.

Schematic representation of scanner adapted from Ledley *et al.* (1974).

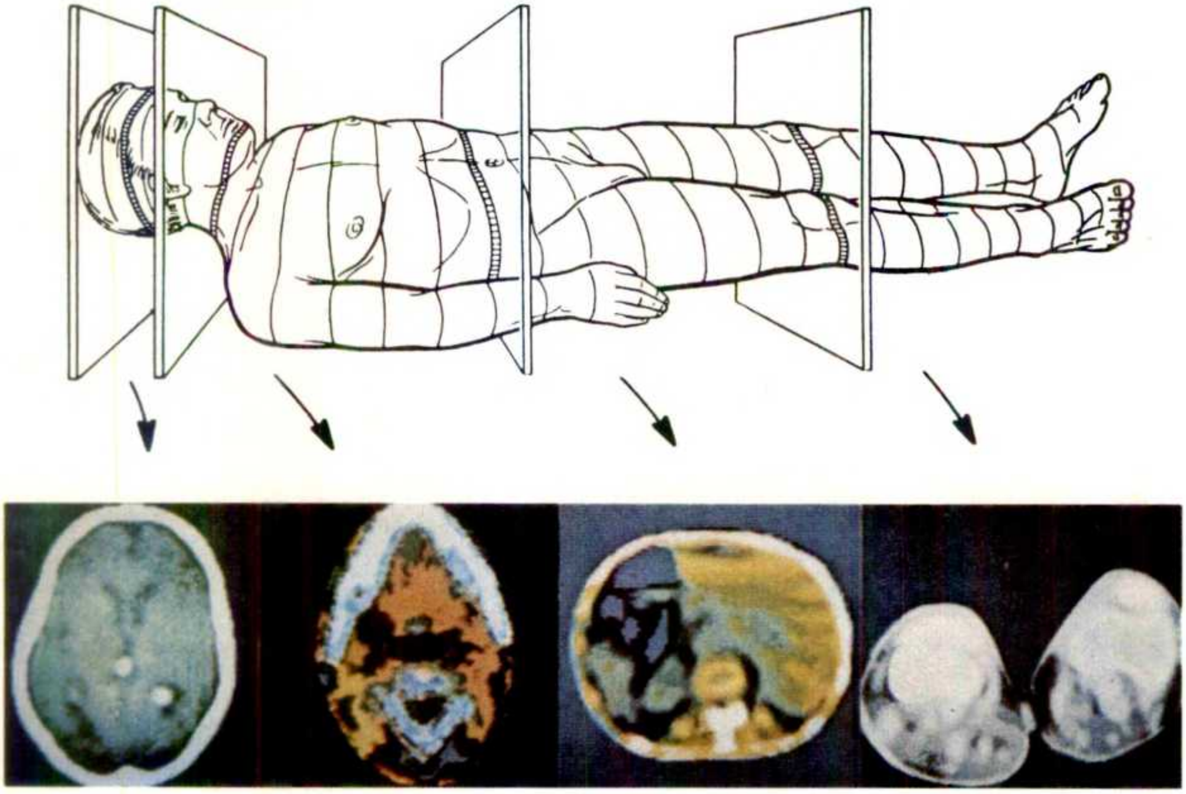

FIG. 2.

Colour sections from the Acta Scanner. Courtesy of Dr. Ledley (1974 and *Science*).

X-ray profile as illustrated in the diagram. The detector X-ray tube assembly is then rotated through a small angle and a second profile is obtained. The process is repeated many many times and the information stored in a computer. If the transmitted intensity is measured very carefully, it is possible to have the computer reconstruct the absorption coefficients of the tissues that are in this plane of interest. It should be noted that no information is contributed to the picture by material which is not in the plane of interest so that much less extraneous and unwanted information is recorded than is the case in conventional tomography. In addition, the scintillation crystal detection system has low noise and sees very little scattered radiation. For the first time we now see a cross-sectional picture of the anatomy which is strikingly similar to pictures in an anatomy textbook.

In the EMI brain scanner, due to Hounsfield (1973), the head is encased in a water-bag so that the pencil beam always passes through some 20 cm of material either in the form of water alone, for points outside the head, or water plus head for points inside the head. The computer determines the absorption coefficient of each element relative to water, yielding so called "EMI-numbers". The first machine reconstructed the density at 80 × 80 points and required about five minutes for the scan and five minutes to create the picture.

This system created immense excitement in radiological circles, and, as of today, EMI has sold nearly 200 such units in the North American continent.

It would be quite out of place for me to discuss this brain-scanner in detail. However, I would like to mention what has happened since the EMI-scanner was reported in December 1973. In October 1974, Dr. Ledley described his ACTA scanner in *Science*, (Ledley *et al.*, 1974). This uses the same principle as the EMI-scanner, but was designed to take sections of all parts of the body, as illustrated in Fig. 2.

The density data is presented in colour. Many radiologists resist colour pictures because they are new and different from the pictures they are accustomed to, but I believe colour adds a real extra dimension to the visualization of organs and that in a few years it will be completely accepted. Immediately, many other companies started to develop their version of the EMI-scanner for all sections of the body.

To obtain a picture with detail, all motion of the patient during the scan must be prevented. In the EMI brain scanner, the head is immobilized by the water-bag. For other sections of the body, breathing

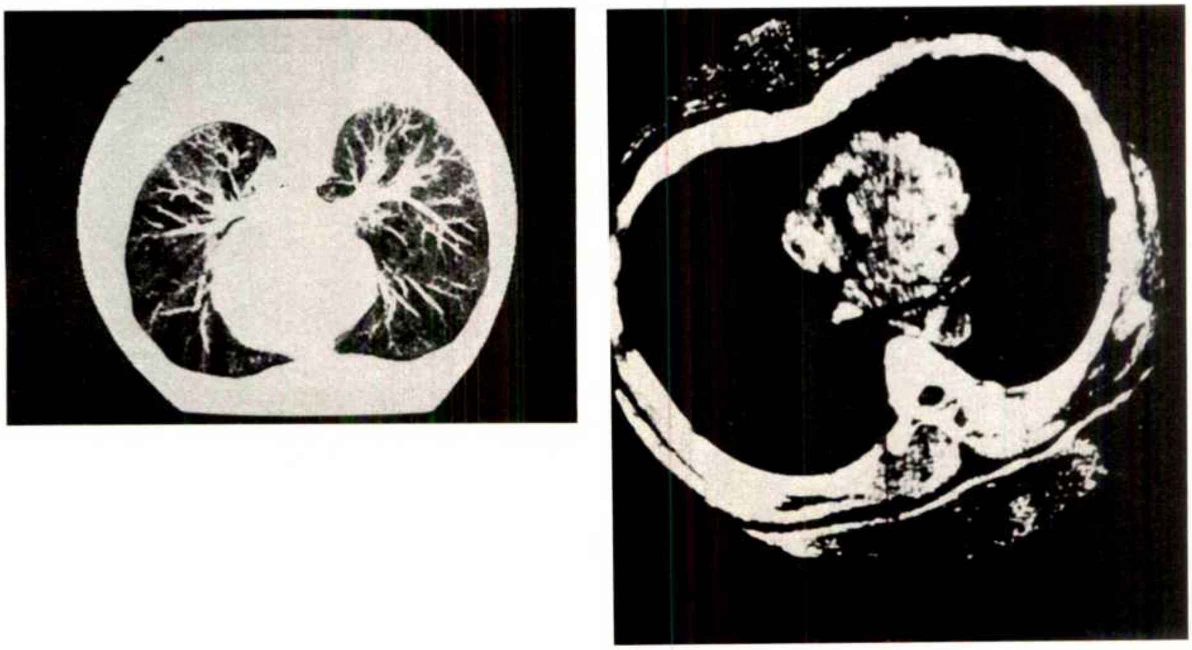

FIG. 3.
EMI-scan of the chest. Courtesy of Mr. Hounsfield.

of the patient and motions of the heart will introduce artifacts unless the scan can be carried out quickly enough to "stop" these motions. All companies are now trying to produce scanners which carry out the full scan in seconds rather than minutes, and in the future we will no doubt see units which can even stop heart motion.

The latest EMI whole-body scanner takes about 20 seconds for the scan followed by about three minutes computing time to process the picture. Figure 3 shows a scan through the chest. The detail is spectacular; the one on the right was adjusted to present details of the heart, vertebrae and ribs, while the one on the left is adjusted to make visible the lower densities of the lung and to show the major blood vessels in the lung. I am told that this is in fact a scan of the chest of Dr. M. Ter-Pogossian of St. Louis.

An EMI-scan of the abdomen is shown in Fig. 4. This shows the aorta, inferior vena cava, parts of pancreas and kidneys, vertebra, and cord. The detail of these scans is spectacular, showing good visualization of the pancreas for the first time.

The details of this improved scanner are not available, but because of the short scan time (20 seconds) we know that complete translation and rotation motions could not both have taken place. In order to obtain the same information in 20 seconds rather then 200 seconds (three minutes), EMI must have used some ten times as many detectors, with a combination of reduced scan and/or reduced rotation. Extending the idea further, if one exposed some 100–200 detectors by a fan of radiation at one instant, as shown in Fig. 5, then the linear motion of the X-ray tube could be omitted altogether, leaving only the rotation motion.

It has been suggested that scanners should be described by a generation number. First generation scanners typified by the EMI brain scanner or the Ledley machine have two motions—translation and rotation—and take some three minutes for a complete scan. The second generation scanner will have only one motion, requiring seconds rather than minutes for a scan with some 100–300 detectors. The new EMI and the new Delta scanner from Ohio Nuclear approach this. They both use multiple detectors (of unspecified number) allowing them to reduce the number of discrete angles at which measurements are taken. In addition, computer programs are being designed to process the data as it is obtained during the scan, so that the reconstructed image can be seen building up as the scan proceeds, with the final picture available at the end of the scan. This is a clinical advantage, since scans seriously affected by motion artifacts can be aborted before completion.

The third generation scanner may have no motions at all and will use multiple sources of X rays and many detectors. One could imagine a circular X-ray tube around the patient emitting many pencils of X rays matched to many detectors. With such a device, all patient motion could be "stopped", and an instantaneous picture obtained, even of the heart. This is a few years away, but it is coming.

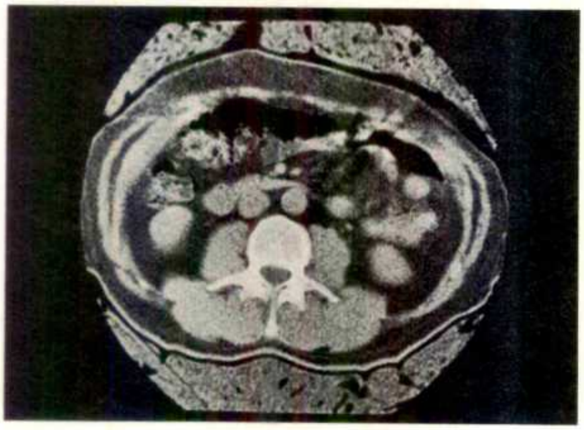

FIG. 4.

EMI-scan of the abdomen at the level of the lower pole of the kidneys. Courtesy of Mr. Hounsfield.

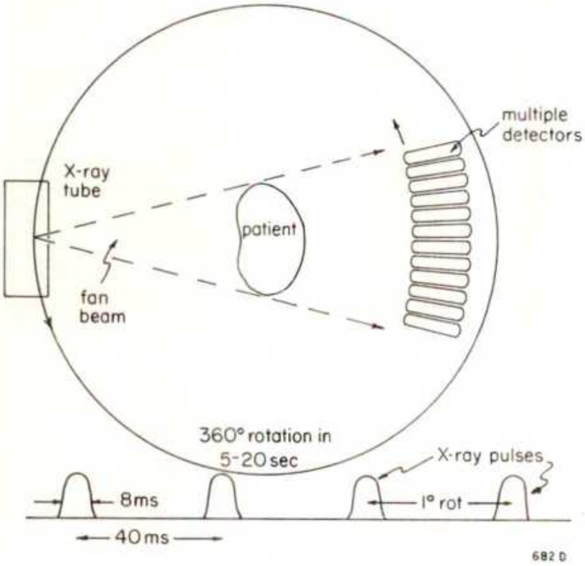

FIG. 5.

Schematic representation of fan beam scanner and pulsed X-ray source.

These are exciting possibilities and many groups of physicists, engineers and mathematicians are working on their version of the scanner. One problem which has interested us in Toronto is the detection system. To date most scanners have used a crystal photomultiplier detector in the current integrating mode—but if many detectors are to be used this is expensive. Furthermore, the actual size of the detectors (1–2·5 cm diameter) prevents adjacent detectors from being packed closely enough together to give the required resolution. They also may have an afterglow problem. If the scan is very rapid, readings adjacent in time can affect each other unless the scintillation from a detector is quenched rapidly. This means scintillators other than NaI must be found. An alternative to the crystal photomultiplier is to detect the radiation with high pressure xenon chambers. We have looked at this problem.

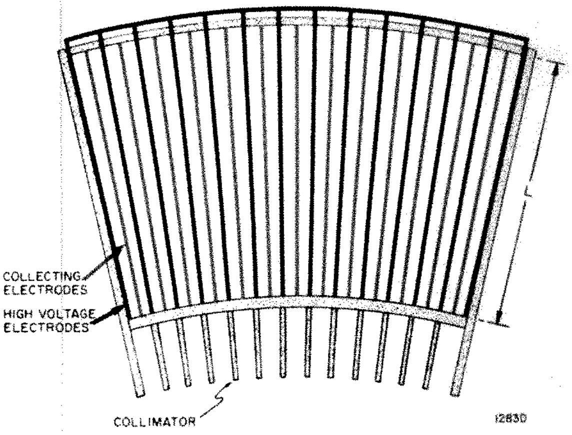

Fig. 6.
Schematic diagram of xenon detectors used in a fan geometry.

High-pressure xenon chambers

Figure 6 shows one design. Adjacent detectors are some 6 mm apart at 140 cm from the source, each subtending an angle of about 0·2 deg. at the source. The ions are collected on the central plane electrode spaced some 3 mm from the two high-voltage plane electrodes. The high-voltage electrodes act as separators between the detectors, preventing the secondary radiation from one affecting the next. Scatter from one pencil of radiation is prevented from entering the next detector by the thin lead septa in the collimator. By using high-pressure xenon, one has a system that is some 1,000 times as sensitive as an air wall ion chamber of the same volume, but, of course, less sensitive than the crystal photomultiplier combination.

However, because of this sensitivity these detectors introduce a serious problem, for with the high ionization density which may be necessary in a scanner it is difficult to collect all the ions. That this is true can be seen from the saturation curves of Fig. 7, which were plotted by Yaffe in our group from data due to Boag *et al.* (1975). They give the current produced in the first 3 mm of the chamber when the entrance window has an area of 1 cm^2. The total current from one of the radial detectors can be found by integrating along one of the radii taking into account the exponential absorption of the radiation by the high pressure xenon.

The three panels give results for three exposure rates. The highest exposure rate (2R/second) corresponds roughly to that which can be produced by a *pulsed* diagnostic X-ray machine operating at 140 kVp and 300 mA with the detectors 140 cm from the source. The second panel gives data for a similarly placed X-ray tube operating at about 30 mA and corresponds to the systems used on most of the current scanners. We see that at high exposure rates the curves cross, showing that at high pressures, although more ions are produced, in fact fewer are collected because of recombination. These results suggest that a pressure of less than 10 Atm has some advantages since the ionization intensity is spread over a larger volume, and essentially full absorption can still be achieved by increasing the radial length *L* (Fig. 6) of the chamber. Figure 7 also indicates some of the difficulties in designing a system which is accurate over a large exposure-rate range as would be the case in a fan beam scanner when the pencil of radiation misses the patient at one angle and is blocked by the patient at another. To overcome this problem it may be necessary to use bolus to "build" the patient into a cylindrical-shaped structure. There is a suggestion that the EMI-scans of Figs. 3 and 4 were taken using such bolus since material is visible on the anterior and posterior surfaces of the subject.

Scattered radiation in fan scanners

When a fan beam is used rather than a pencil beam the question immediately arises as to whether radiation from the fan will produce an appreciable amount of unwanted scattered radiation in the detectors, *i.e.* if one pencil of radiation will affect the next. To answer this question experimentally is not easy, so we resorted to calculations which were carried out by Yaffe in our group. We found that with a collimator 10 cm long designed to give a beam $0{\cdot}5 \times 2{\cdot}00$ cm at the detector at 140 cm, single scatter by a phantom increases the response by 0·16 per cent while double scatter increases it a further 0·06 per cent. Scattered radiation is therefore not a problem.

X-ray sources

Scanners as they are made today put very strong demands on present X-ray source technology. The first-generation machines have used continuous 120 to 140 kV X rays, usually from a highly stabilized d.c. source delivering about 30 mA. This is about as much power as any modern X-ray tube can handle on a continuous basis. To produce a good second generation machine, it may be advantageous to have about ten times this output, and to pulse it. A number of X-ray companies are developing special tubes and generators for scanners.

Computer reconstruction

Mathematical algorithms to reconstruct images from projection data have been available for many years and have been applied to diverse fields of science from astronomy to electron microscopy. They are now being developed specifically for the CAT scanner and a review of this subject is now available (Gordon and Herman, 1974). Algorithms designed specifically for handling data from machines with scans and rotation motions are now being altered to deal with the second generation scanners using fan geometry (Genna, 1975). These programs use the convolution method (Ramachandran and Lakshminarayanan, 1971) and are designed so that data is processed as it is collected, so that less storage is required. Many of the new scanners give the output a few seconds after the end of the scan. Great care has to be taken in designing these algorithms so that they make efficient use of computers, otherwise a very large and very fast computer becomes necessary. A number of them use "micro computers" with special solid-state circuits hard

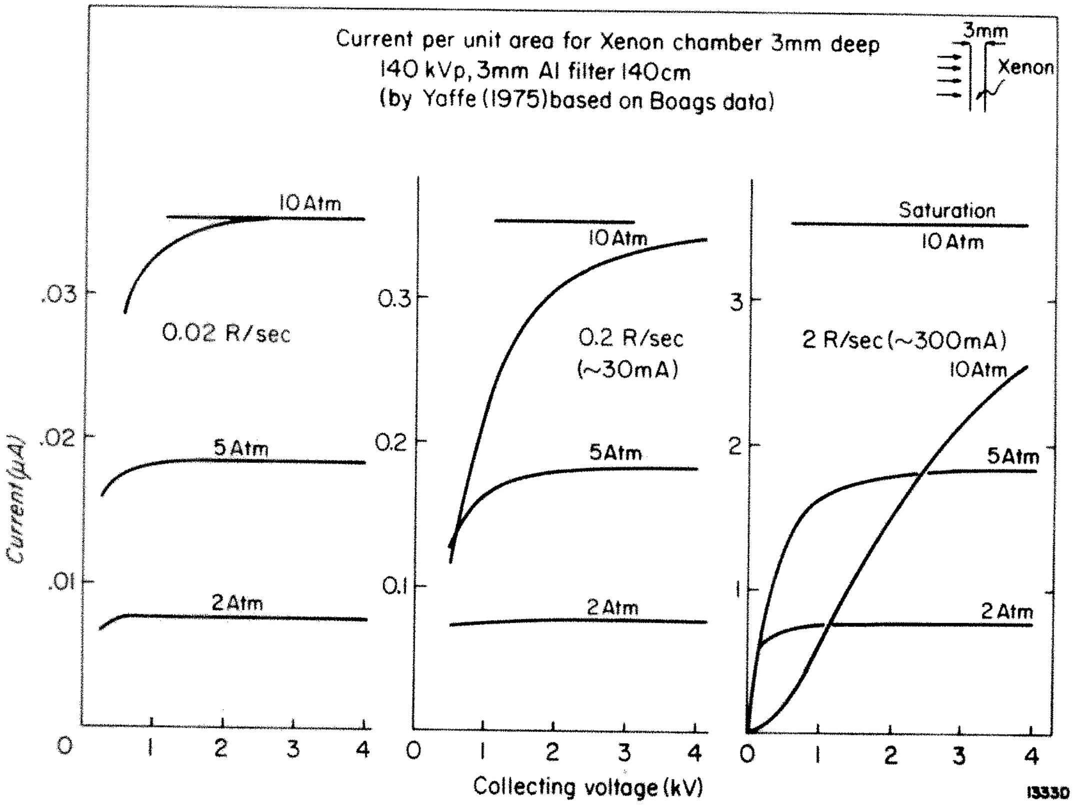

Fig. 7.

Saturation curves determined by Yaffe in our group from data due to Boag *et al.* (1975). Data are plotted for a chamber of 1 cm^2 area and 3 mm deep.

wired into the system to minimize computer time. The algorithms are designed to minimize artefacts.

One artefact which has created considerable interest has been the apparent increase in density just inside the skull suggesting that grey matter has a larger absorption coefficient than white matter which is in the interior of the brain, although no physical explanations could be found for this. Gado and Phelps (1975) have shown that this is a computing artefact and that as expected these tissues have the same absorption. Such artefacts will probably disappear with better algorithms.

X-ray spectrum

The fact that the radiation from an X-ray beam is not monochromatic introduces some problems in the interpretation of the data. This problem has not been solved.

Display

The optimum display method and the place of colour is yet to be determined. This field is in its infancy.

Value of brain scanning

The EMI brain scanner is the only scanner whose clinical value has been investigated extensively. Neuroradiologists on the North American continent agree that brain scanning is the diagnostic tool of choice to investigate many neurological disorders. Not only is the technique non invasive, but it may replace unpleasant and hazardous procedures necessitating hospitalization. Elimination of the latter can alone justify the purchase of such machines. For example Wortzman *et al.* (1975) have demonstrated that in the Toronto General Hospital the EMI brain scanner "saves" 2 million dollars per year in bed space and neurological procedures. These can be allocated to other services. A present estimate by Wortzman (Bermuda, 1975) is that there should be one such scanner for each half million people. It should be emphasized that the diagnostic value of the scanner can often be increased greatly by intravenous infusion of contrast material specifically for scanning.

Value of whole-body scanning

Now what can we expect from whole-body scanners which can look at all sections of the body in relatively short times? To try to answer this question, two Delta scans given to me by Mr. Steve Maloney of Ohio Nuclear are shown in Figs. 8 and 9. The first (Fig. 8) shows a hepatoma of the liver which can be seen in reduced tissue density in the left lobe (right-hand side). The scan also shows the spleen, one kidney, the aorta, vertebrae and cord. The ribs are also clearly visible.

Figure 9 is another section of the abdomen showing the aorta, inferior vena cava, bowel, and the major psoas muscles; an air artefact is shown in the bowel.

The possible uses of such scans are obvious. They may be of great value in detecting small tumours. The scans to date suggest that it is not unrealistic to hope that tumours 1 cm³ in size may be made visible. Scanning may then become a powerful diagnostic tool. Already we know that larger tumours can be seen and these could be studied as a function of time as the tumour is treated with radiation or chemicals leading to real advances in radiotherapy

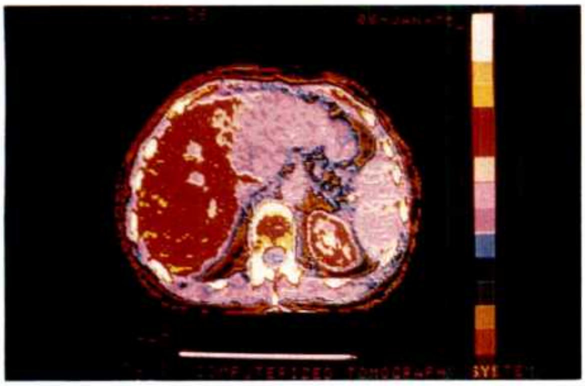

FIG. 8.

Scan obtained on Ohio Nuclear Delta scanner, showing a hepatoma of the liver in the left lobe, spleen, one kidney, aorta, vertebrae and cord. Courtesy of Mr. Steve Maloney.

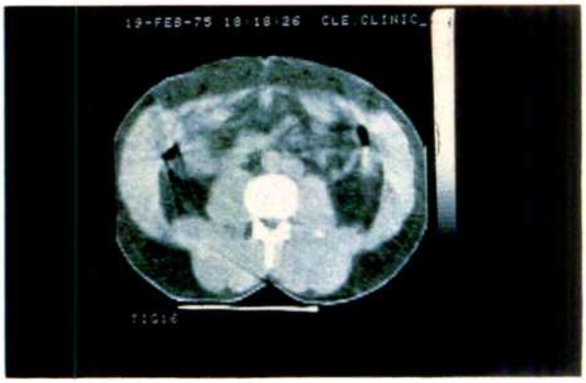

FIG. 9.

Section of the abdomen showing aorta, inferior vena cava, bowel and the major psoas muscles.

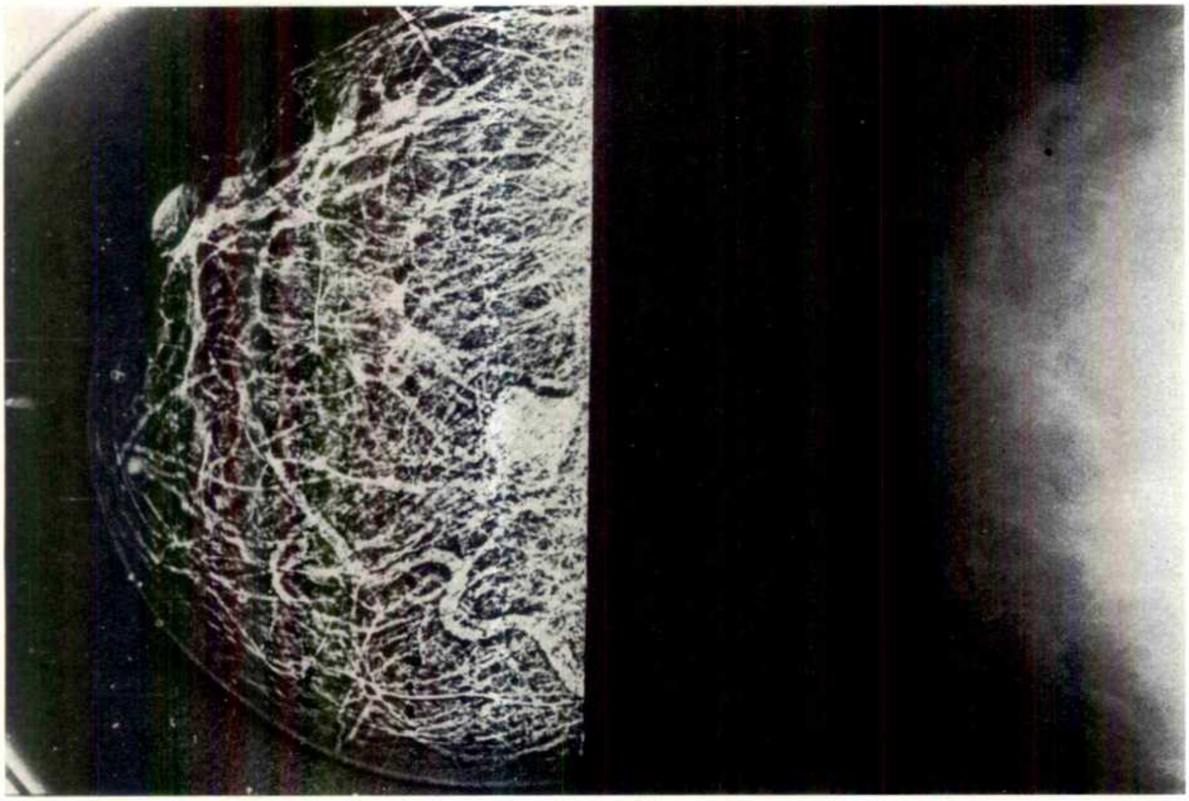

FIG. 10.

Radiographs of a breast taken by xeroradiography, left, and by standard film techniques, right. Comparison is really not fair for the film picture, since it would show more if it were viewed by transmitted light. Courtesy of *B. J. R.*, Boag *et al.* (1972).

and chemotherapy. Finally, visualization of tumours and normal tissues in juxtaposition will be of great value in radiotherapy treatment planning. The densities of the tissues determined by scanning will make possible accurate dosimetry and corrections for inhomogeneities in a realistic way. Further, it should decrease the chances of geographic misses and enable the radiotherapist to observe the effects of radiation on the tumour during treatment. One can envisage connecting the output of the scanner to radiotherapy treatment programs in order to predict true dose distributions in practical situations.

Compton scanner

There are other ways of producing scans. For example, it is possible to determine the density of tissues at a point in the plane of interest by measuring the amount of radiation scattered by the Compton process. Such a device has been developed by Clarke (1975) and is now being tested by Battista and Bronskill in Toronto. In this device a pencil of radiation from a cobalt source is directed towards a point in the patient and the scattered radiation is detected at an angle of 45 deg. The amount of radiation emitted at this angle depends on the density of the tissue at the point of interest P, the attenuation of the primary beam in reaching P, and the attenuation by the patient of the scattered beam in escaping from P. With this device, it is possible to make many measurements as the pencil of radiation "looks at" a matrix of points in the plane of interest. It is too early to say whether or not such a device will compete with the CAT scanners. It has one major advantage in radiotherapy treatment planning, since it will measure electron density directly and this density determines the absorption of the high-energy treatment beams used most commonly today in radiotherapy. One can envisage such a scanner

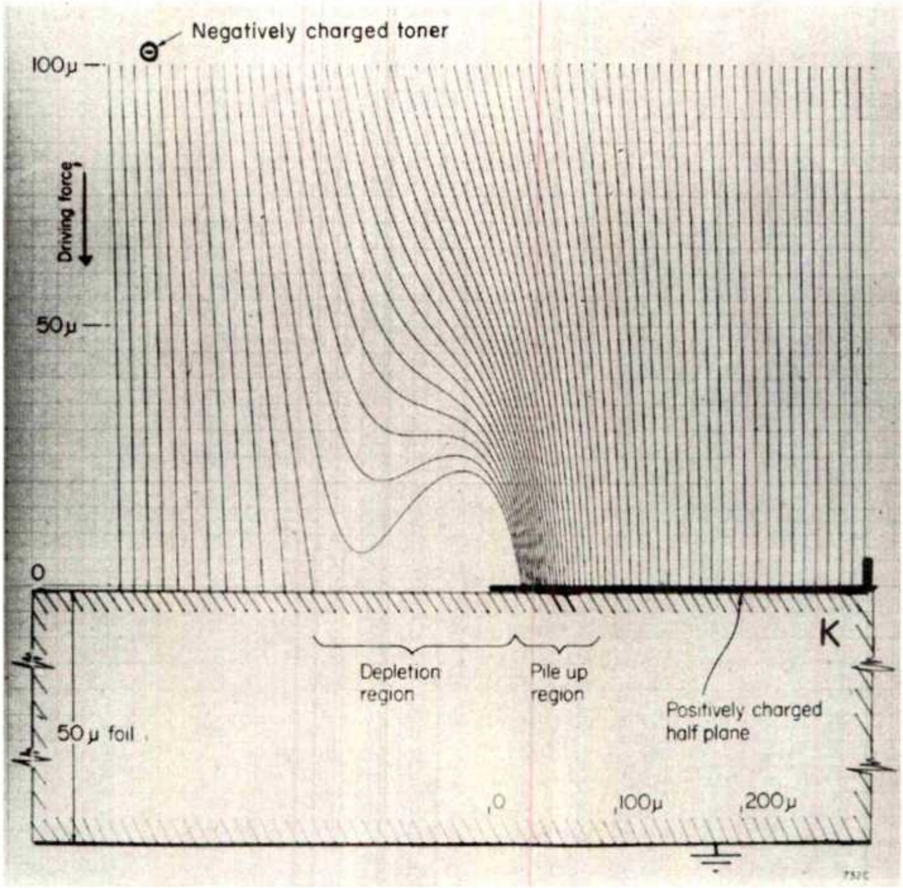

FIG. 11.

Calculated trajectories of powder particles near charge discontinuity. The parameters of the calculation were:
Toner diameter $= 5\ \mu$m
Toner charge $= -8{\cdot}0 \times 10^{-17}$ coulomb/particle.
Air viscosity $= 1{\cdot}83 \times 10^{-4}$ poise.
Bias field $= 500$ V/cm.
Surface charge density $= +1{\cdot}0$ nC/cm^2.
Foil dielectric constant $= 3{\cdot}3$.

connected to a computer which would carry out the treatment planning directly without requiring conversion first to density and then to dose.

Summary of scanners

In summary, then, I look forward to a number of years of very active development in the field of scanners. We can expect them to be useful in diagnostic procedures, in radiotherapy planning, and in evaluating treatment by studying the change in size of tumours as a function of treatment and time after either radiation or chemical agents. Scanners are indeed a very exciting addition to the techniques which are available to the radiologist and radiotherapist. We can expect to find them in all diagnostic radiological departments, large radiotherapy departments and chemotherapeutic units.

ELECTROSTATIC IMAGING

Xeroradiography

With this brief summary of computer-assisted tomography, I will now turn to recent developments in electrostatic imaging and in particular xeroradiography and ionography. In xeroradiography, the image is recorded on a charged selenium plate and is made visible by placing the plate in a powder cloud so that the charged toner particles adhere to the charged plate. The powder pattern can be transferred to a sheet of paper giving a blue copy which is viewed in ordinary light, or it can be photographed and presented as a black-and-white picture. Xeroradiographic units were developed many years ago, but it is only recently that they have been made reliable enough to be used routinely in radiological examinations.

On the North American continent xeroradiography has been popularized mainly through the work of Wolfe (1969; 1972), and of Wolfe *et al.* (1971). In Great Britain extensive investigations have been carried out by Boag (1973; 1975a, 1975b) and associates, Boag, *et al.*, (1971; 1972) and James *et al.* (1973). Xeroradiography has been used mainly in examinations of the breast and to a lesser degree the extremities of the body such as the arms and the legs.

The main reason for the popularity of xeroradiography in breast examinations is due to the phenomenon of edge contrast. This is illustrated in Fig. 10 which shows a picture of the breast by xeroradiography and by standard film techniques. The comparison is really not fair because the film should be looked at with transmitted light, but even with this reservation the differences are spectacular. One notices that lines appear to be drawn around all the structures of the breast, making the tumour easily visible. Several years ago, I had the opportunity of visiting Dr. John Wolfe in Detroit with Dr. Rideout, our radiologist. Dr. Wolfe gave Dr. Rideout a pile of xeroradiograms of the breast and suggested that he examine the pictures and come to his own diagnosis, and then compare his diagnosis with that of Wolfe's. I kept Wolfe's diagnosis hidden and Dr. Rideout explained to me some of the thought processes of a radiologist as he endeavours to make a diagnosis. After each diagnosis we compared his results with the written report by Wolfe. I was impressed as the two doctors came to the same diagnosis in 29 out of the 30 breast xerographs. Dr. Rideout came away from this two hour session convinced that diagnosis made by xeroradiography was more accurate than by current available techniques with film. I came away from the session impressed by the difficulty faced by the radiologist in interpreting diffuse patterns. Shortly afterwards, we were able to obtain from Xerox one of their new xeroradiographic systems.

Xeroradiography is useful in outlining tissues where there is very little contrast, but the system does not accurately record differences in X-ray intensity. That this is so can be seen from Fig. 10, where the intensity well outside the breast seems to

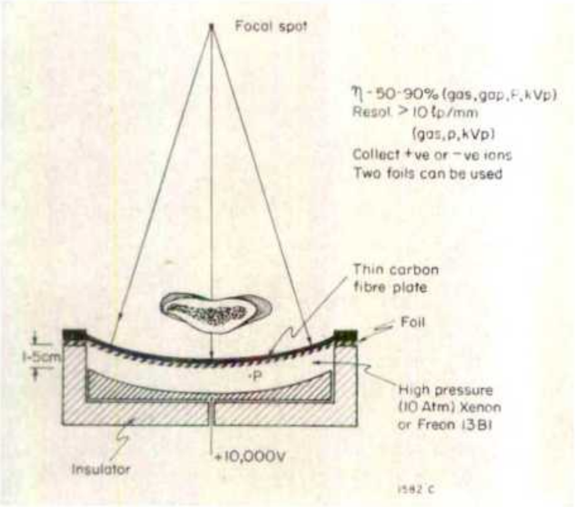

FIG. 12.

Schematic diagram of high pressure ionography chamber. The charged pattern is formed on an insulating foil stretched under the upper electrode, whose centre of curvature is at the focus of the X-ray tube.

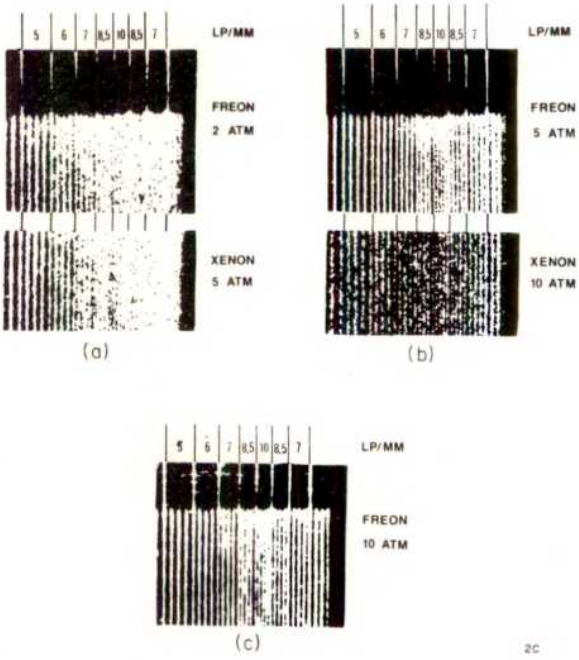

FIG. 13.

Powder pictures of test pattern (Nuclear Assoc. 07–553) taken at 64 kV with a 1 cm gap in the chamber and 30 kV/cm collecting field.

(a) Xenon at 5 atm (9·5 mR) compared to freon at 2 atm. (60 mR).

(b) Xenon at 10 atm. (6·0 mR) compared to freon at 5 atm. (30 mR).

(c) Freon at 10 atm. (18 mR).

be comparable to the much reduced intensity corresponding to the thickest part of the breast, next to the ribs.

Why does edge contrast occur when electrostatic images are produced? To answer this we must understand the powdering process. Figure 11 shows the calculated trajectories of negatively-charged toner particles as they are driven by an electric field toward a foil on which is a uniformly deposited positive charge over half of an infinite plane. The calculations of trajectories by Plewes (1976) are complex, taking into account the viscosity of air, the size and charge of the particle and the detailed determination of the electric field using the method of images (Plewes and Johns, 1975). Notice the scale of the diagram—we are looking at trajectories in the region from zero to 100 μ above the foil. In the regions remote from the edge the trajectories are almost parallel and of equal concentration, so that the same number of powder particles reach the uncharged portion as the charged part. However, near the edge, there is a fringing field due to the lines of force which curve from the charged surface to the grounded surface below the plate. When particles enter this region they are swept sharply to the right and piled up on a region just inside the edge of the charged region. Thus, wherever there is discontinuity in the charge pattern, there will be a depletion region where powder is removed and a pile-up region where powder is concentrated.

The edge contrast shown in this diagram is only present if the half plane of charge is partially developed, that is, if only a small fraction of the charges on the half plane are neutralized by the charges on the toner particles. If development is carried out to completion, a process which requires very long powdering times, then the edge contrast all disappears. When liquid toners are used development is usually to completion; the liquid system is more sensitive, but the edge contrast disappears.

Ionography

The main disadvantage of xeroradiography is the fact that it is about a twentieth as sensitive as the best film plus screen technique and it is for this reason that its use has been confined to examinations of the extremities. In the autumn of 1971, Dr. Boag and I attempted to find a more sensitive system which would have all the advantages of edge contrast. We first attempted to develop further an avalanche device based on work done originally by Reiss and Lange (1973). We regretfully came to the conclusion that at the present state of knowledge it probably would not work well. We then developed a system which we have called ionography, and on which we have published extensively (Johns *et al.*, 1974;

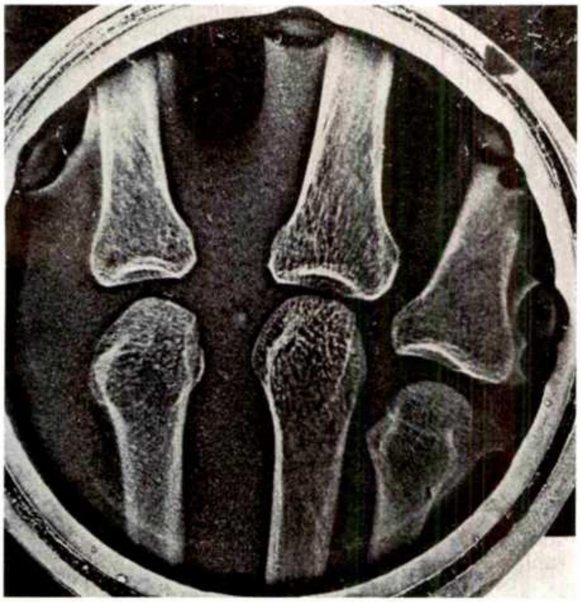

FIG. 14.

Picture of part of the hand taken at 50 kV with 50 μm foil and an exposure to the hand of 25 mR.

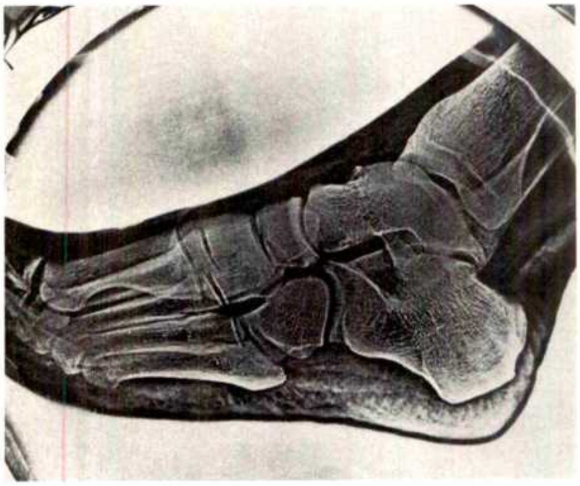

FIG. 15.

Picture of foot taken with the 25 cm imaging chamber at the Institute of Cancer Research, Sutton.

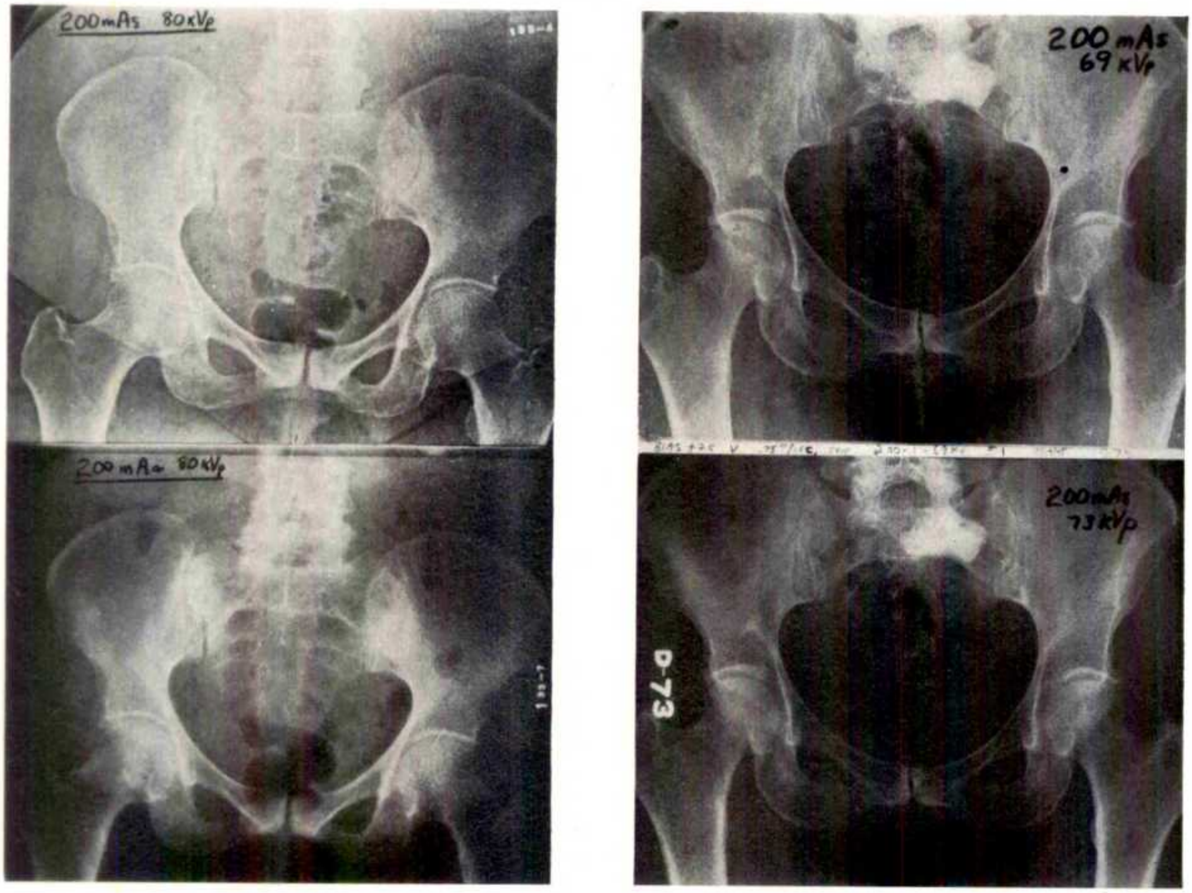

Fig. 16.

Radiographs of the pelvis by the group at Hahnemann Hospital, Philadelphia, on ERG equipment supplied by Xonics, courtesy of Drs. Brady and Stanton.
Upper left — 200 mAs, 80 kV, ERG – powder cloud development.
Lower left — 200 mAs, 80 kV par speed film by conventional methods.
Upper right—200 mAs, 69 kV, ERG, liquid toner bias 25 V.
Lower right—200 mAs, 73 kV, conventional film techniques.

Fenster, Plewes and Johns, 1974; Johns, Fenster and Plewes, 1975; Johns, Plewes and Fenster, 1975a; Boag, 1975a, 1975b). We believe the system we have developed is essentially the same as the process known as electron radiography (ERG) developed by Xonics (Proudian *et al.*, 1974) and tested clinically by Brady and Stanton and their associates (Stanton *et al.*, 1972, 1973a, 1973b, 1974, 1975). This field of ionography or electron radiography has developed very rapidly. Our interest in this problem has been centered mainly around the principles involved.

The basic idea of ionography is illustrated in Fig. 12 which shows a high pressure ionography chamber. It consists of two spherical electrodes whose common centre of curvature is the focal spot of the X-ray tube. The gap of 1–5 cm between the electrodes is filled with a high pressure, high atomic number gas such as xenon. The foil on which the picture is to be taken is placed underneath the top curved surface; the foil must be clean and highly insulating. After attenuation in the object to be radiographed, X-ray photons are absorbed in the high-pressure gas. On absorption at a point such as *P*, high-energy electrons may be emitted in any direction from the point of interaction. If the gas is at a high pressure and is dense, these travel only a fraction of a millimetre so that the ionization is deposited in a small region about *P*. If these ions are collected along the direction of the X rays then no smearing of the pattern takes place as they are propelled towards the foil. This condition is achieved when the lines of force are coincident with the direction of the X rays, that is when the electrodes are spherical and have as their common centre of curvature the focal spot of the X-ray machine. After the charges are deposited on the foil, the chamber is opened and the foil developed as one would the selenium plate in xeroradiography. The foil itself with deposited toner particles becomes the record. Smearing of the pattern by diffusion is not a problem provided positive ions are collected rather than the negative carriers which are electrons in ionized xenon. If it is desired to collect negative charges a small amount of O_2 is added which scavenges electrons giving negative ions. Also, to be useful, the ion chambers should absorb most of the X-ray energy, and the front plate of the chamber should be of such material that it does not attenuate the X-ray beam, especially the soft X rays which are useful in producing the image of thin sections. Further, a high enough voltage should be used so that sensibly all the ions are collected. These conditions can all be satisfied (Fenster *et al.*, 1974; Johns *et al.*, 1974).

Resolution

Calculations show that, with a gas such as xenon under a pressure of ten atmospheres, the electrons set in motion by diagnostic X rays produce some 50 per cent of their ionization in a region of radius about 0·2 mm about P, the point of interaction, so that high resolution is possible.

Pictures of a resolution chart taken under a variety of conditions using two types of imaging gases are shown in Fig. 13. It is seen that a resolution of ten line pairs per millimetre is easily achieved. Freon 13B1 (containing a bromine atom) is a good alternative gas to xenon, especially for imaging soft X rays.

Figure 14 shows a picture of part of a hand taken at 50 kV with a 50 μm foil and an exposure to the hand of 25 mR. Very good detail is visible.

Figure 15 shows a picture taken on Professor Boag's 25cm chamber at Sutton. It is actually a picture of his own foot.

Ionography with commercial equipment

For the past three years Brady, Stanton and their associates at the Hahnemann Medical Centre in Philadelphia have been using prototype equipment made by Xonics in routine radiology. This group has shown that ionography referred to by them as ERG (electron radiograph) is a practical method of obtaining diagnostic information. Figure 16 shows four pictures of the pelvis taken by this group. The two on the left give a comparison of film and ERG using powder cloud development, while the two on the right compare standard film technique with ERG using development by liquid toner. Both ERG pictures show slightly more detail than the picture obtained by film. ERG with powder development requires a smaller exposure than film. Development with powder cloud shows more edge contrast than development with liquid toner.

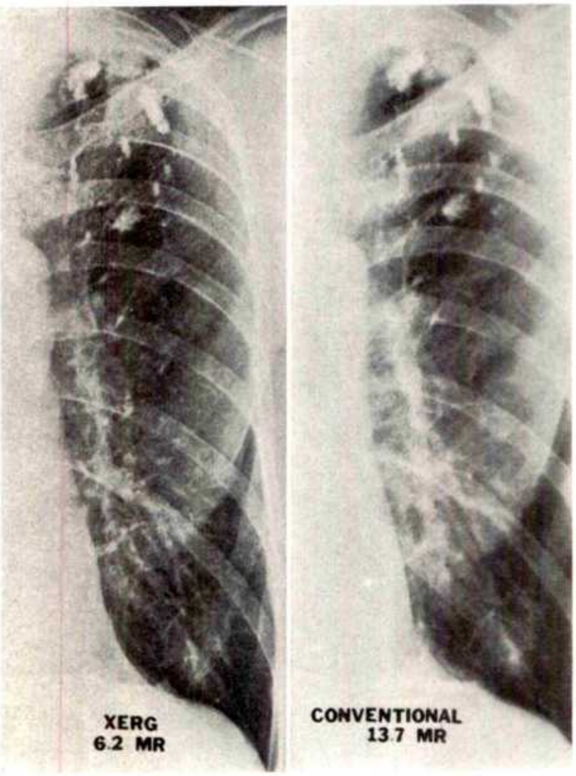

FIG. 17.

Chest pictures taken by electron radiography, left, and conventional methods, right, using the Xonics automatic chest unit. Courtesy of Dr. E. P. Muntz.

Figure 17 shows pictures taken at the University of Southern California Medical Centre, under the direction of Dr. George Jacobson, using electron radiographic equipment supplied by Xonics.

These examples should convince one that good pictures of diagnostic value can be obtained by ionography. Ionography using liquid toner is more sensitive than film and gives some edge contrast. When the system is altered to give more edge contrast it becomes slightly less sensitive than film. Xonics have produced a practical system which can take and process an ERG picture of the chest in

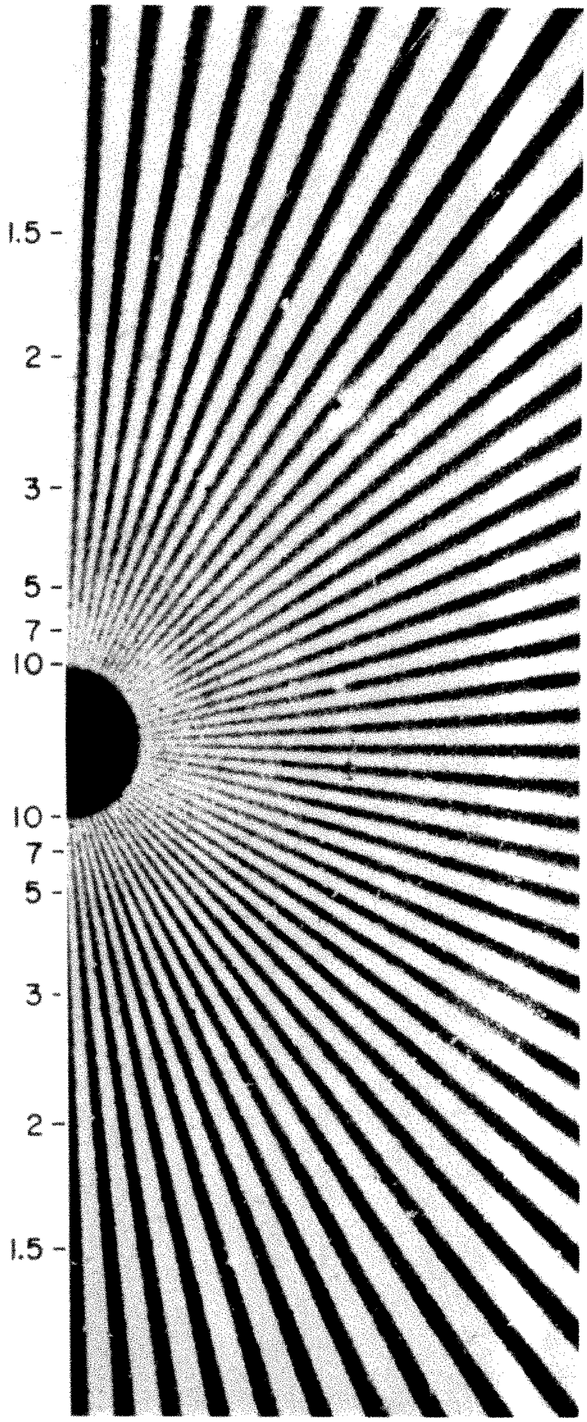

Fig. 18.

Enlargement of a powder picture of test pattern (Nuclear Assoc. Inc. Model 07–510) taken at 65 kV with a 4 mm electrode separation, 30 kV/cm collecting field, 15 mR exposure, and a foil of 125 μm thickness. Resolution given in line pairs per millimetre to the left of the picture. Courtesy of *Medical Physics* (Fenster and Johns, 1974).

about a minute. They are now developing a special unit for mammography. Only experience will determine the practical value of these systems in radiology.

Recent new developments

In the time I have left, I would like to discuss some new ideas which may be of value in ionography. One system which Aaron Fenster of our group has investigated is the use of a liquid instead of a gas as the absorbing material in the chamber (Fenster and Johns, 1974). When liquids are used the gap between the electrodes can be made very much smaller because the liquid has a higher density than a gas. One requires a liquid with high atomic number and very high resistivity, so that the charged pattern once formed will not be discharged. We found that tetramethyl tin is a good liquid for an ionography chamber; it is not toxic, the tin gives it a high absorption and the picture taken by this method is shown in Fig. 18.

It is instructive to compare the operation of a chamber filled with liquid and one filled with gas. In the gas a very high voltage is required to produce saturation, but in a liquid an even higher voltage is required, and in fact, it is impossible to get an electric field high enough to separate all the ions as they are produced in a liquid. Ions of opposite signs are initially produced so close together in a liquid that recombination occurs before they can be separated. This is illustrated in Fig. 19.

With xenon there is a fairly good saturation region which occurs at about 20 kV/cm whereas in tetramethyl tin there is no sign of any saturation in this

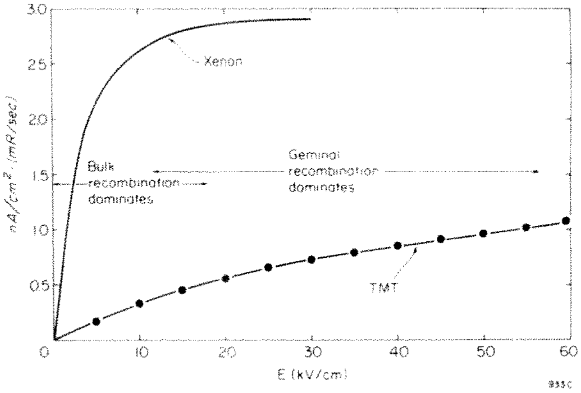

Fig. 19.

Typical ionization currents as a function of electric field for gaseous xenon at 10 atm. in a 1 cm gap and the liquid TMT at 1 atm. in a 4 mm gap for X rays generated at 80 kV. Courtesy of *Medical Physics* (Fenster and Johns, 1974).

curve which would continue nearly to the top of the graph—if a high enough field were used. The liquid is not quite as sensitive as the xenon because of the difficulty of collecting the ions. The layer of liquid actually absorbs more of the X rays than the xenon but only some 30 per cent of the ions can be collected. The main advantage of the liquid chamber is that a pressurized system is not required and the front electrode of the system can be made thin. No commercial companies have developed a liquid ionography system.

Application of liquid ionography in nuclear medicine

With a liquid system it is possible to absorb in a relatively thin layer the radiations used in nuclear medicine. One could envisage then a liquid system consisting of a flat chamber the size of a patient so

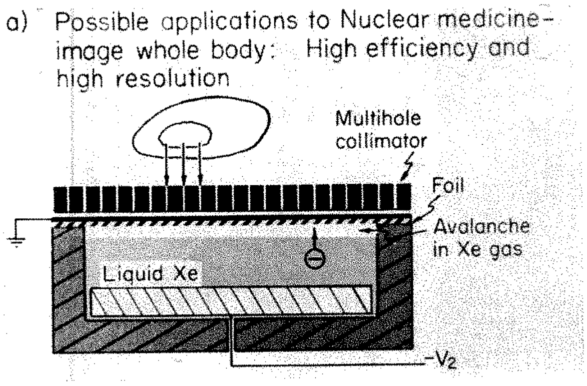
a) Possible applications to Nuclear medicine– image whole body: High efficiency and high resolution
Multihole collimator
Foil
Avalanche in Xe gas
Liquid Xe
−V₂

FIG. 20.

Schematic diagram showing possible application to nuclear medicine. The chamber is filled with liquid xenon with a gaseous layer on the top in which a controlled avalanche is produced.

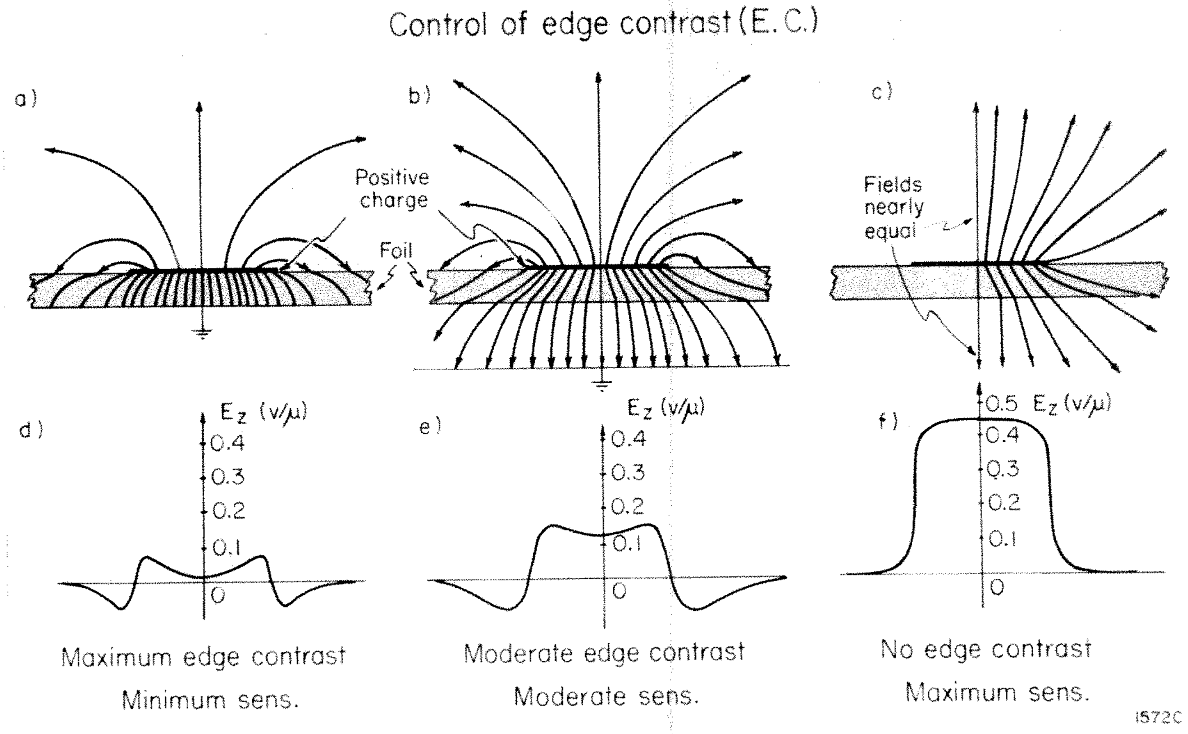

FIG. 21.

Schematic diagram showing a method to control edge contrast.

(a) Grounded metal surface on the back of the foil.

(b) Grounded metal surface a small distance from the foil.

(c) Grounded metal surface removed a large distance from the foil.

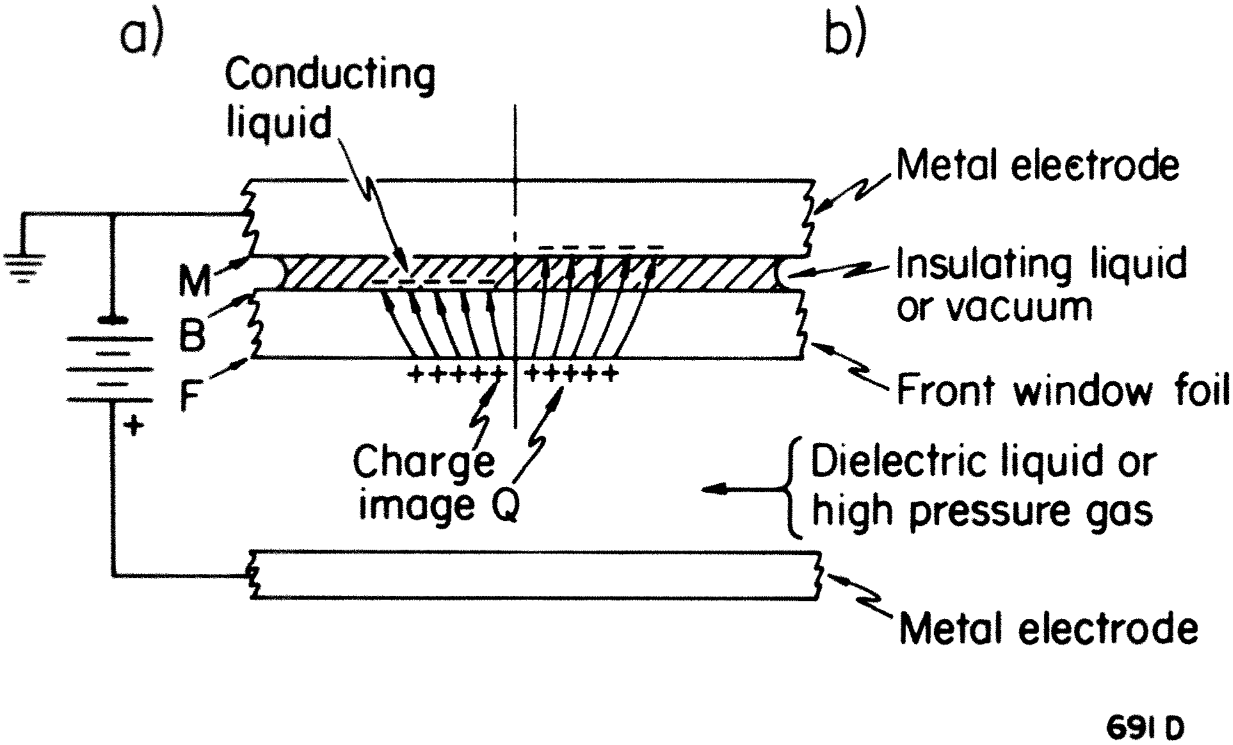

FIG. 22.

Front window electrode configurations used in ionography. The space between the front window foil and front electrode is filled with conducting liquid in (a). (b) shows the space either evacuated or filled with an insulating liquid. (See Plewes, *et al.*, 1975.)

that the whole of the patient could be imaged on a foil at one time. One possible design of such a system is shown in Fig. 20.

On the absorption of a photon from ^{99}Tc^{m} about 10^4 ions are produced. If these ions could be made to produce an avalanche of gain 100 in the space above the liquid, individual photons would be imaged with high resolution on the foil. To my knowledge no one has yet attempted to build a chamber to the design shown in Fig. 20, but there is some indication that such a device might be feasible (Zaklad *et al.*, 1972).

Edge contrast

It would be a great advantage to radiologists if a single X-ray exposure could give rise to two or three foils, each developed with a different amount of edge contrast. Figure 21 shows how the edge contrast depends upon the distance between the charge pattern and the grounded plane. In xeroradiography one cannot possibly change this distance since it is determined by the thickness of the selection plate. However, in ionography this can be altered at will by changing the thickness of the foil. When the distance is very small, as in Fig. 21a, edge contrast is maximized. The vertical component of the electric field has the distribution shown in Fig. 21d. It is the reversal in the electric field at the edge which gives rise to trajectories of the toner particles which were illustrated in Fig. 11. If the grounded plane is moved back from the foil, or if a thicker foil is used, then the edge contrast is minimized, as shown in Fig. 21b and 21e. Finally, if the grounded foil is removed completely, all edge contrast is lost (21c, f). Thus one can change the edge contrast in ionography by merely altering the distance to the ground or the thickness of the foil. It should be noted that when edge contrast is minimized the electric fields are larger and the system more sensitive.

Closed system ionography

We have found a way to read the charge pattern on the inside of the foil from outside the chamber so that the system can remain closed. To do this one

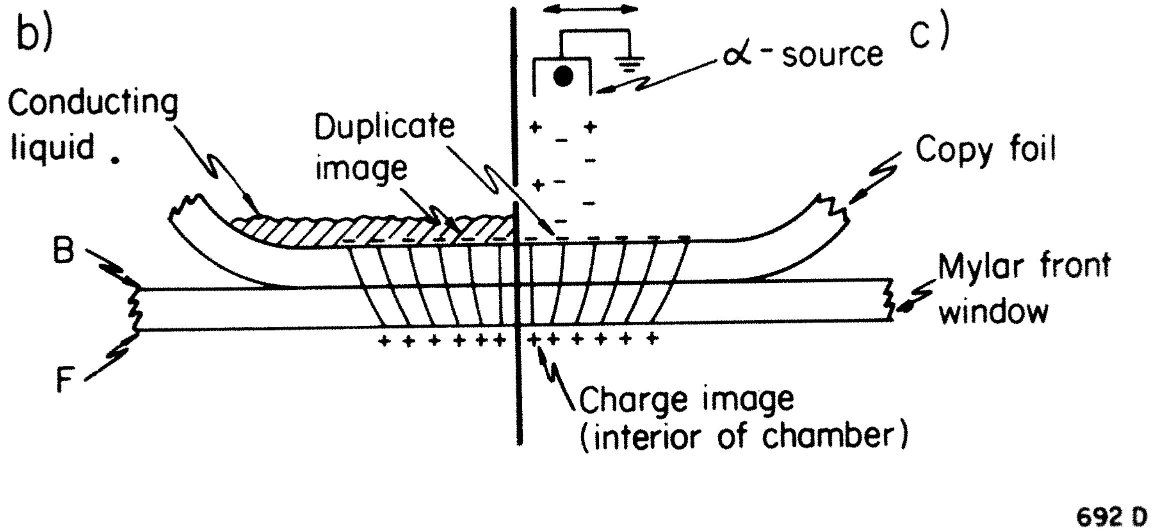

FIG. 23.
Diagram to illustrate the transfer process using a conducting liquid (left), and an alpha source (right) to ionize the air above the foil.

must expose the chamber using the electrode configuration shown in Fig. 22b rather than the usual one of Fig. 22a. During exposure (Fig. 22a) a high voltage is maintained between the metal electrode at ground and the metal electrode on the lower part of the chamber. The metal grounded electrode can be coupled to the foil by a thin layer of conducting volatile liquid such as alcohol. When this liquid dries, the negative charges corresponding to the positive charges are left on the upper surface of the foil. This is the normal way in which ionography chambers have been used. The foil has a positive charge put on the inside surface through the action of the X rays and a negative charge of almost the same magnitude and distribution appears on the back surface of the foil during the exposure. It can, however, be arranged, as shown in Fig. 22b, where the conducting liquid is replaced by an insulating liquid or a vacuum. During the exposure the negative charges will appear on the metal electrode. If after exposure this metal electrode is carefully stripped away from the front window foil, there will be positive charges on the inside of the chamber but no corresponding negative charges on the opposite side of the foil. The electric field from these positive charges reaches through the front window of the chamber into the space above the chamber as illustrated in Fig. 21c. This electric field then can be used to read the charge pattern from outside.

How this is done is shown in Fig. 23. After the exposure is complete, a second foil or copy foil is placed on the mylar front window foil, and the space between them evacuated so that contact is good. A conducting liquid is then added as shown on the left, or the air in the space above the foil is ionized as shown on the right. In both cases negative charges are deposited on the upper surface of the copy foil. These will be a very good reproduction, but of opposite sign, of the charge pattern on the inside of the chamber. This copy foil can now be removed and developed, with the desired amount of edge contrast.

Since the original charge pattern has not been disturbed a second foil can then be placed on the original and "read" again, and this can be repeated as often as required. Finally, after enough copies have been made, the charge on the inside of the chamber can be removed by exposing the chamber to X rays with no electric field in the chamber. Detailed calculations (Plewes *et al.*, 1975) show that very little resolution is lost by this process provided the total thickness of the two foils is 50 μm or less.

The system described above is particularly applicable to liquid ionography since the front of the chamber is very thin. Our liquid chamber has been used to carry out closed system ionography (Fenster and Johns, 1976). Figure 24 shows pictures of a small part of the hand copied four times from the outside of the liquid ion chamber and developed with different amounts of edge contrast. The method makes ionography a very practical alternative to

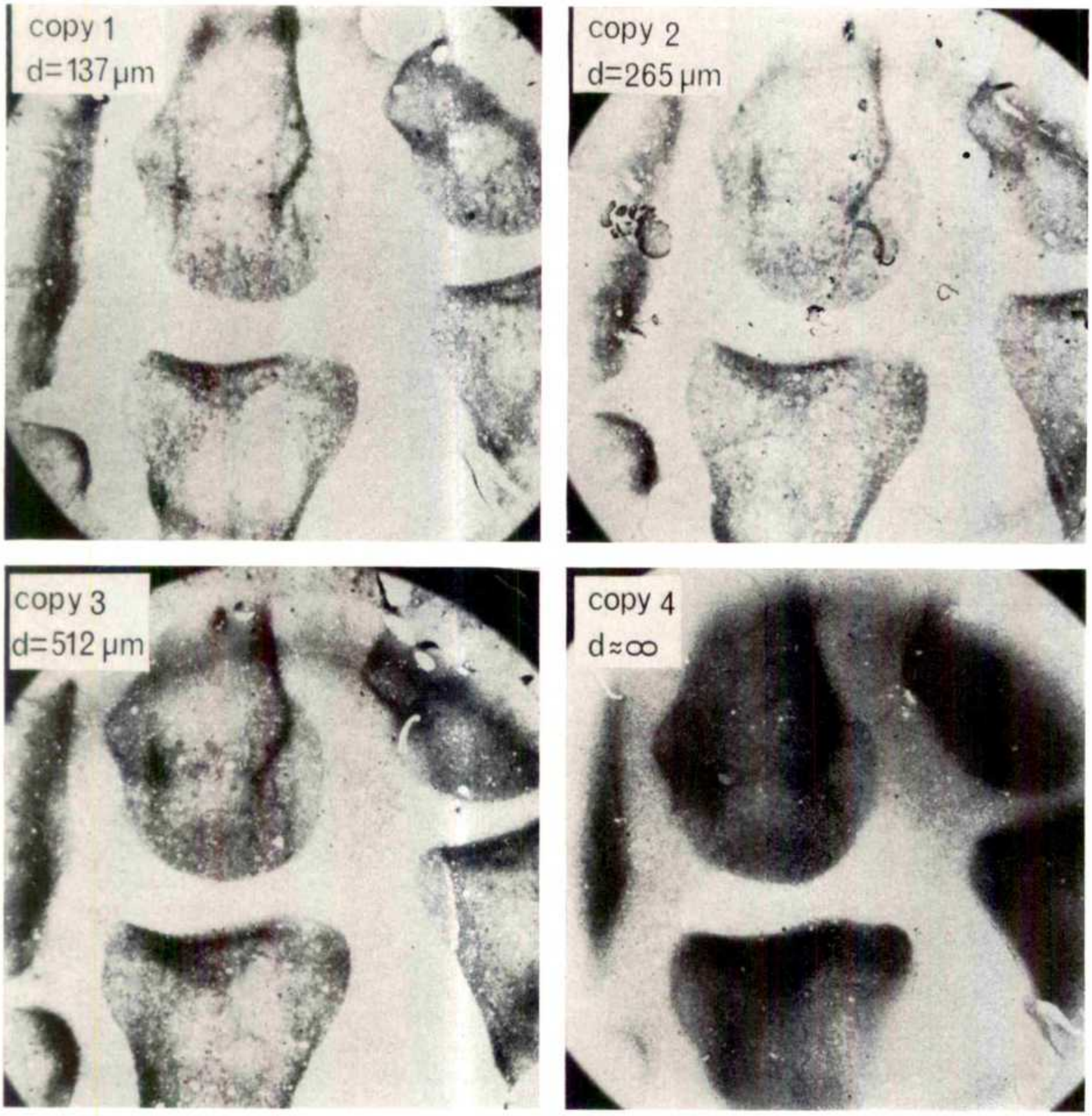

FIG. 24.

Radiograph of part of a hand copied four times from the outside of the liquid TMT ion chamber. Each copy developed with different amount of edge contrast. Radiograph taken at 54 kV with an exposure of 45 mR, electric field inside the 4 mm chamber of 42·5 kV/cm.

conventional methods using films since one exposure gives the radiologist a number of copies whose edge contrast is under *his* control.

Sensitivity

Xonics have shown that their electron radiography system is slightly more sensitive than film plus screen combinations. However, their pictures show very little edge contrast, and the question must be asked whether the advantages of electron radiography are worth the trouble if the picture has no edge contrast. The argument is often given that radiologists do not want edge contrast. I think that too much edge contrast can certainly confuse the radiologist, but I believe several pictures from one radiograph are required each with different amounts of edge contrast to help in the visualization of small soft-tissue tumours. I believe the system which I have described could be developed commercially to do this. However, this introduces a problem, for if one has edge contrast then one loses sensitivity. This needs further study; careful comparisons of the sensitivity of xerographic systems, gaseous and liquid ionography systems and films with modern screens should be carried out.

Summary

Ionography is a system which offers high resolution, sensitivity, and the possibility of obtaining multiple copies giving various amounts of edge contrast. The science is in its infancy, and many new ideas are being considered. The development of a solid-state device of sensitivity greater than selenium, which would have many of the properties of high pressure xenon and none of its disadvantages, would be a major breakthrough. I am also sure that the Xerox company is looking for ways to increase the sensitivity of their selenium plates. We may hope that some of these new techniques will offer the radiologist an advantage in the detection of small soft-tissue tumours.

CONCLUSION

In this lecture I have dealt with two new methods of imaging, methods which I am sure will have a great impact on the practice of diagnostic radiology. Someone else could equally well have shown the details of how ultrasonics can be used in medical diagnosis. Still another expert in nuclear medicine could have described the trends that are taking place in that field where impressive technical advances are continually being made. Many of these fields overlap and supplement each other. I envisage hospitals of the future establishing departments of imaging which will include all of these ways of obtaining diagnostic information as well as other ways yet to be discovered. Such a department would be "problem oriented" rather than "technique oriented", as the term "radiology" implies.

Such a department would require complex equipment of considerable sophistication, and such sophistication raises a number of serious problems. First, the cost of such devices increases with their sophistication, and in the present era of Government control new techniques must be justified. This has been done already for the EMI brain scanner. The second problem arises through the sophistication itself. To give useful results, the machine must be operated at maximum efficiency. This requires someone with expertise working on the local scene, and is analogous to having highly competent physicists and technical people in a hospital where high energy linear accelerators are used for radiotherapy. In my opinion, the only satisfactory way to get this expert ability is to have hospital-based physicists, engineers and methematicians.

I envisage this group of experts comprising a department of "Medical Physics and Engineering" placed, geographically, midway between oncology and imaging departments. Such a group of applied scientists will not only keep the equipment operating correctly to ensure quality control, but will also be a source of new ideas and developments for these two departments. Already some hospitals are moving in this direction.

ACKNOWLEDGMENTS

I am indebted to the National Cancer Institute of Canada and the Medical Research Council of Canada for continued support on many of these research projects. I am grateful to Dr. A. Fenster and Mr. D. Plewes for many discussions concerning the problems of ionography and tomography, and for their excellent experimental and theoretical work. I am indebted to many people who have discussed these problems with me, in particular, Dr. Rideout, head of the Radiology Department at the Ontario Cancer Institute, Dr. Ray Bush of the Radiotherapy Department, Dr. Michael Bronskill of the Nuclear Medicine Department, Dr. Kenneth Taylor at the Toronto General Hospital and Professor J. W. Boag of the Institute of Cancer Research, Sutton.

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Erratum

FETAL CERVICAL HYPER-EXTENSION IN BREECH PRESENTATION, by J. G. B. Russell and Margaret R. C. Aird (July 1976, p. 580).

It has been brought to our attention that the paper by R. G. B. Russell and Margaret R. C. Aird which appeared in the July issue of The British Journal of Radiology when printing was incorrectly titled Fetal cervical hypertension in breech presentation.

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A simple new formula for relating changes in renal length to changes in renal volume

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ABSTRACT

A simple new formula for relating changes in renal length to changes in renal volume is derived. It is not assumed that the kidney is any given shape, but it is assumed that a kidney does not change its shape when it enlarges. It is shown that the fractional change in renal volume equals three times the fractional change in renal length plus three times the fractional change in renal length squared. Examples of applications of the formula using figures for changes in renal length, published elsewhere in the literature, are given for renal hypertrophy in both childhood and adult life and for volume changes during excretion urography.

Although it is difficult to calculate absolute renal volumes accurately (Griffiths *et al.*, 1975), changes in renal volume can in fact easily be assessed. It is shown below that the fractional change in renal volume approximates to three times the fractional change in length plus three times the fractional change in length squared.

DERIVATION OF FORMULA

The fundamental assumption made is that an enlarging kidney does not change its shape. Evidence for this is provided by the fact that renal length has been shown to correlate well with the cube root of the mass (Griffiths *et al.*, 1975). The enlarging kidney will thus increase its diameters in proportion. Hence, the volume of the kidney will be proportional to the cube of its length (Laufer and Griscom, 1971).

Let L = length of kidney
and X = change in length of kidney
then X/L = fractional change of length of kidney
and $(L+X)$ = new length of kidney
first volume of kidney $= KL^3$ where K is a constant
final volume of kidney $= K(L+X)^3$

Fractional change in volume

$$= \frac{\text{final volume} - \text{first volume}}{\text{first volume}}$$

$$= \frac{K(L+X)^3 - KL^3}{KL^3}$$

Hence it can be shown that

$$= 3\left(\frac{X}{L}\right) + 3\left(\frac{X}{L}\right)^2 + \left(\frac{X}{L}\right)^3$$

$\frac{X}{L}$ is the fractional change in length and is easily measured. In fact, for changes in length of up to 30 per cent $\left(\frac{X}{L}\right)^3$ makes a difference of less than 1 per cent and can be ignored.

Hence fractional change in volume is approximately
3 × fractional change in length
+3 × fractional change in length squared.

By measuring the fractional change in length the fractional change in volume can always be deduced.

For instance consider a kidney 14 cm long enlarging by 1 cm. to 15 cm. long. The fractional change in volume will be $3 \times \frac{1{\cdot}0}{14} + 3 \times \left(\frac{1{\cdot}0}{14}\right)^2 = 0{\cdot}23$ or 23 per cent.

DISCUSSION

It is very difficult to measure absolute renal volume at all accurately. Renal width measurements vary with quite small degrees of rotation (Griffiths *et al.*, 1975) and renal depth measurements are very difficult to make. Further it has to be assumed that the kidney is a particular shape such as an ellipsoid; this may not be true. This formula depends only on renal length measurement. This can be measured accurately and is the best parameter of renal size *in vivo* (Klatte *et al.*, 1972; Griffiths *et al.*, 1975). Further no assumption need be made about the original shape of the kidney. This formula can also be applied to any enlarging organ that does not change its shape.

EXAMPLES

Using figures for changes in renal length published elsewhere, it can be shown that renal volume may increase by 12 per cent during an intravenous urogram (Wolpert, 1965), by up to 30 per cent in adult renal hypertrophy (Boner *et al.*, 1972; Orecklin *et al.*, 1973, Dossetor, 1975) and by 100 per cent in renal hypertrophy in childhood (Laufer and Griscom, 1971).

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Book review

Textbook of Nuclear Medicine Technology. By Paul J. Early, Muhammad Abel Razzak and D. Bruce Sodee, pp. 496, 2nd edn., 1975 (Saint Louis, C. V. Mosby, Distributed by Henry Kimpton, London), £10·40.

In the second edition of this book the authors have attempted to expand the contents to correspond to the growth of nuclear medicine. New chapters have been added on computer fundamentals, modulation transfer function, $^{99}\text{Tc}^{\text{m}}$ biorouting and radio-immunoassay. Dosimetry has been enlarged and given its own chapter, and the one on radinuclide therapy rewritten. There have also been revisions and small changes in the remainder of the text. The alterations have increased the length by nearly a third, and the price is not unreasonable for the size and quality of the book, although rather high for individual purchasers.

The book is written as a text for nuclear medicine technologists and is divided into two parts: nuclear science and clinical nuclear medicine. In nuclear science the level of treatment makes it suitable for radiographers, technicians and doctors entering the field. The chapter on dosimetry is a welcome addition. The subject is plagued by different approaches, symbols and terminology, and here the work of the Medical Internal Dose (MIRD) Committee has provided an excellent methodology and comprehensive sets of data; it is this approach which has been adopted. However, the initial discussion of the classic expressions of Marinelli can only lead to confusion, while the lack of a simple explanation of the method and some of the basic terms is a pity. The chapter on computer fundamentals is clear but readers turning to this chapter for help in understanding manufacturers' literature, or to learn something about the application to nuclear medicine, will be disappointed. The other new chapter in the nuclear science section is an excellent introduction to modulation transfer function. It can be recommended to anyone who gives up at the mention of MTF!

The first part is clearly written and very well illustrated but some of the deficiencies of the first edition still exist. The section on the Anger Camera has been expanded but not sufficiently in view of the importance of this type of equipment in nuclear medicine. Also lacking is an adequate discussion of the relative merits of cameras and scanners. No mention is made of digital scanners.

The second part, clinical nuclear medicine, has a useful new chapter on $^{99}\text{Tc}^{\text{m}}$ biorouting which goes some way towards remedying the lack of discussion on radiopharmaceuticals. However, there is only a short section on the fundamentals of nuclide generators, with insufficient treatment of build-up, yield and elution characteristics. A clear and valuable chapter on radio-immunoassay is the other addition to this part of the book.

It is a serious omission that no mention is made of ^{67}Ga citrate for tumour localization and only the briefest statement is given about ^{123}I for thyroid investigations. The topic of lung studies with gases is dealt with in two paragraphs. There are also other topics which have not been brought up to date: for example, in discussing pancreatic scanning with ^{75}Se selenomethionine only the brief statement '. . . and recently subtraction techniques' is made. Space has been unnecessarily devoted to anatomical diagrams which could be found in any standard anatomy text.

The valuable additions to the second edition are marred by the dated nature of some of the other material, especially on the clinical side. Many chapters of the nuclear science part can be commended but it is difficult to understand the choice of some of the material in the clinical part. This is a book which departments concerned with nuclear medicine should have for selective use.

P. H. S. SMITH.

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Thallium 201 chloride uptake in tumours, a possible complication in heart scintigraphy

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(*Received January, 1976*)

ABSTRACT

An abnormal uptake pattern of ^{201}Tl thallous chloride observed during myocardial scintigraphy of a patient with known thoracic tumour localization suggested the possibility that thallous chloride may also accumulate in tumours. This was confirmed by observing ^{201}thallous chloride accumulation in rhabdomyosarcoma implants in rats.

Thallium 201 accumulation in tumour cells should be borne in mind as a possible complicating factor when using this reagent for the evaluation of cardiac conditions in oncological patients.

Thallium 201 in the form of thallous chloride is becoming widely used for myocardial imaging. The thallous ion behaves as potassium in the body and thus localizes preferentially in the myocardium. Ischaemic and necrotic areas show as cold spots.

We have recently been using this reagent combined with transmission scintigraphy of the thorax for the evaluation of pericarditis in oncological patients. In the case reported here the possibility arose that there was ^{201}Tl uptake in tumour tissue. To confirm this the uptake of ^{201}Tl chloride in rat rhabdomyosarcoma was studied.

CLINICAL DATA

The patient, a 47-year-old male with a bronchus carcinoma in the left lung, was referred for combined transmission/thallium scintigraphy for the investigation of pericarditis. The scintigrams obtained are shown in Fig. 1.

The scintigrams were made with the aid of a Nuclear Chicago HP gamma-camera using a 140 keV high-resolution collimator. In the first instance an antero-posterior transmission scintigram was prepared (Fig. 1, upper left) with the aid of a ^{57}Co flood field source (Amersham) to delineate the boundaries of the mediastinum. Subsequently, with the patient in the same position, the heart blood pool was visualized by means of intravenously injected ^{99}Tc^{m} albumin at a dose of 1·0 mCi (Fig. 1, upper right). Finally, a 2 mCi dose of ^{281}Tl chloride was administered intravenously to visualize the myocardium. The scintigram was prepared by scanning on the energy of the mercury X rays (80 keV) 30 minutes post-injection. Under normal circumstances a preferential uptake can be seen in the ventricles with only a trace of atrial activity due to the relatively small amount of atrial muscle present.

In this case the thallium scintigram (Fig. 1, lower) shows an area in the left lung, to the side of the ventricular region, with preferentially increased activity. This can be seen on the right side of the scintigram. Within a few days of the study the patient died. Post-mortem examination confirmed the presence of a poorly differentiated squamous cell carcinoma in the left lung in a situation corresponding to the region with increased activity on the thallium scintigram and infiltrating into the myocardium. There would appear to be a definite indication of ^{201}Tl uptake in tumour tissue.

The localization of ^{201}Tl in rat rhabdomyosarcoma

In order to check these observations the uptake of thallium in rat rhabdomyosarcoma implants (TNO) was investigated in a pilot study. A group of four rats implanted with rhabdomyosarcoma (TNO) were injected with 0.1 ml. of ^{281}Tl chloride injection (Philips Duphar) intravenously via a tail vein. This corresponded to a dose level of 100 μCi per rat. Thirty minutes post-injection, the optimal time for thallium localization in the myocardium, the animals were sacrificed and the thallium concentration in tumour, liver, skeletal muscle, myocardium and blood was determined. The results are given in Table I.

TABLE I

THALLIUM 201 CHLORIDE CONCENTRATIONS 30 MINUTES POST INJECTION IN ADULT RATS (AVERAGE OF FOUR ANIMALS)

Tissue	Thallium 201 concentration (% injected dose per G wet tissue)	Tissue/blood ratios
Tumour	0·43	8·6
Liver	0·70	14·0
Skeletal muscle	0·16	3·2
Myocardium	2·42	60·5
Blood	0·05	—

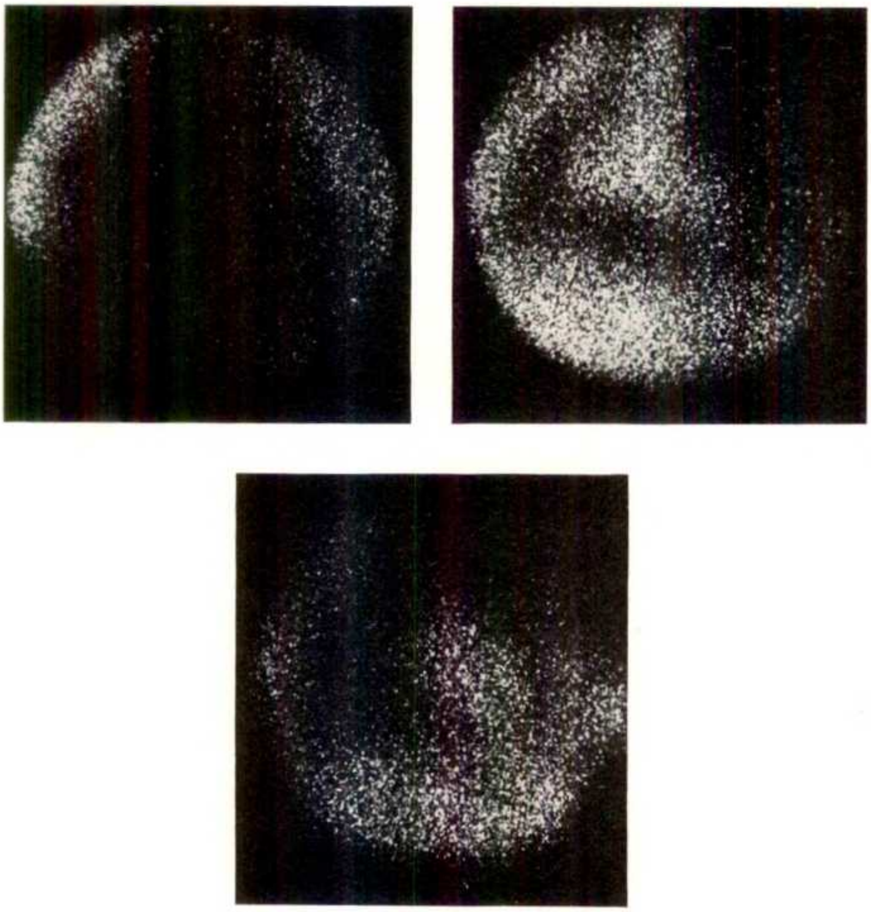

Fig. 1.

Transmission and heart scintigram. Upper left, antero-posterior transmission scintigram of mediastinum. Upper right, heart blood pool visualized with technetium albumin and lower, ^{201}thallium scintigram of the myocardium showing uptake in the lung associated with tumour.

Discussion

The results of the pilot study in rats confirm the preferential uptake of ^{201}Tl in myocardium and liver, but also clearly demonstrate a significant accumulation of activity in the tumour tissue. There is little doubt that this is also the case in the clinical example. It is clearly desirable to bear this possibility in mind when interpreting thallium scintigrams of patients with tumour localizations in the lungs or mediastinum.

The possibility that ^{201}Tl has an affinity for tumour tissue would seem to be unlikely any more than is the case with mercury, gallium or indium complexes. A more likely explanation is that the thallium uptake is due to an increased cell membrane permeability to ionic substances in tumour cells as would appear to be the case with a number of other ionic tumour localizing reagents (Cox and Van der Pompe, 1975; 1976).

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Pharmaco-cholangiography with anticholinergic drugs in the dog

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ABSTRACT

The effect of atropine and pipenzolate bromide (PB) in different dosage levels was investigated in intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes in six cholecystectomized dogs (20–36 kg) equipped with Thomas cannulas through which the common bile duct could be cannulated. Doses of 1 mg atropine and 20 mg PB, half the dose given intravenously just prior to the contrast agent and the other half with the iodipamide infusion, had the greatest effect in decreasing the bile flow (atropine—24% at 60, PB—23% at 30 minutes) and increasing the bile iodine concentration (atropine + 16%, PB + 14%). The biliary iodipamide excretion rate was not affected.

Opacification of the biliary tree during intravenous cholangiography is dependent on the total number of iodine atoms in the ducts struck by the X ray beam. Improvement of intravenous cholangiography can be attempted by either increasing the rate of biliary contrast material excretion or by increasing the contrast material concentration in the bile through decreased bile fluid production. Anticholinergic drugs are known to diminish bile fluid production (Preisig *et al.*, (1962); Erlinger and Preisig (1969)) and if they do not alter the biliary contrast material excretion rate, a higher bile iodine concentration and consequently better bile duct opacification could be expected.

We investigated two anticholinergic drugs, atropine sulphate and pipenzolate bromide in various dosages for their potential to improve intravenous cholangiography in the dog.

MATERIALS AND METHOD

The investigation was conducted on six male mongrel dogs weighing 20–36 kg (average weight: 26.4 kg). They were prepared by cholecystectomy and implantation of a modified Thomas cannula (Thomas, 1941), which allowed cannulation of the common bile duct under direct vision. At least a two week period was allowed for recovery from surgery.

The dogs were given only water for 24 hours prior to each investigation. General anaesthesia was induced with 25 mg/kg sodium pentobarbital (Nembutal Sodium®, Abbott Laboratories, North Chicago, Illinois) intravenously and maintained throughout the examination with a constant drip infusion of 50 μg per minute per kilogram body weight. Under fluoroscopic control, a green Kifa catheter was passed via the femoral vein into the inferior vena cava and its tip placed below the entrance of the renal veins. This was used for drawing blood samples.

Blood samples taken at the beginning of each study were analysed for bilirubin, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase, and occasionally for urea nitrogen (BUN) and creatinine. Samples taken before and at intervals during the procedure were analysed for iodine concentration.

A Foley-type catheter was inserted into the bladder and the urine was collected over the three-hour period of each study, and at the end of the study the bladder was flushed with distilled water until the returning fluid was water-clear. The iodine concentration of the urine plus bladder washings was determined.

An 8 French Foley catheter was introduced into the common bile duct via the Thomas cannula. The balloon of the catheter was inflated to prevent bile leakage and at the same time to occlude the accessory pancreatic duct. During the entire study, the dog was on his right side at the edge of the table so that bile could be collected by gravity from the Foley catheter into graduated test tubes.

Iodine concentrations of the serum, bile and urine were estimated by the fluorescent excitation technique with ^{241}Am (Moss, *et al.*, 1972).

During periods of bile diversion, the bile salts were replaced by a constant intravenous infusion of 0.5% sodium taurocholate (Nutritional Biochemicals Corporation, Cleveland, Ohio) at a rate of 2 ml. per kg per hour (0.3 μmol/kg per min). After obtaining a steady baseline bile flow, usually, at one to two hours, the actual experiment was started. A preliminary study had suggested the effectiveness of the chosen mode of administration and dosage range of the two investigated drugs. They were studied separately in two sets of experiments.

(A) *Atropine Sulphate* (Elkins-Sinn Inc., Cherry Hill, New Jersey). Each of the six animals received in four experiments in randomized order, 0.6 ml/kg methylglucamine iodipamide 52% (Cholografin Methylglucamine (Biligrafin), Squibb and Sons, Princeton, New Jersey), plus 0, 1, 2 and 4 mg of atropine. The iodipamide was diluted with distilled water to a total volume of 50 ml and infused intravenously over a 30 minute period. Half of the atropine was administered intravenously over a one minute period just prior to the start of iodipamide infusion, and the other half was infused intravenously together with the iodipamide over the following 30 minutes. At least a one week interval was allowed between studies.

(B) *Pipenzolate Bromide* (Piptal, Lakeside Laboratories, Milwaukee, Wisconsin). After completion of the atropine study, the same six animals were again used to investigate pipenzolate bromide in the same fashion. The drug, supplied by the manufacturers in powdered form, was dissolved in distilled water and administered in dosages of 0, 10, 20 and 40 mg in randomized order. Again, half of the dose was given intravenously over a one minute period just prior to the constant material infusion and the other half with the iodipamide over the next 30 minutes.

The results in each of the six animals for each dosage level of the two drugs were combined and expressed as a mean ± one standard deviation.

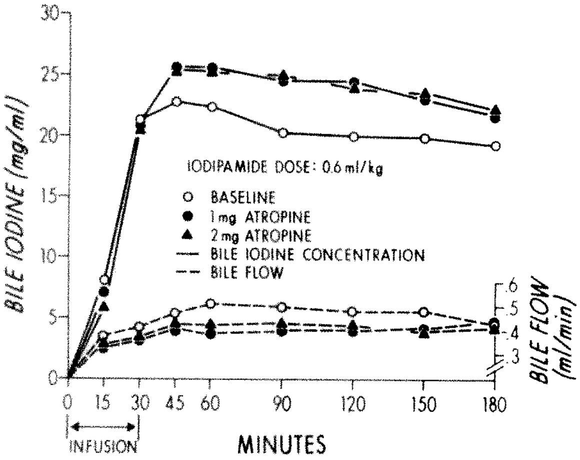

FIG. 1.

Mean bile iodine concentrations and mean bile flow in six dogs during intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and two different atropine dosages. Standard deviations for each value are given in Table I.

Statistical analysis was performed using Student's T-test for paired data.

RESULTS

A. *Atropine Sulphate.* The largest, 4 mg atropine dose had no significant effect on biliary iodipamide excretion or concentration compared to baseline values and will, therfore, not be further discussed in this section. Average values of the baseline studies and the cholangiograms with 1 and 2 mg of atropine are shown in Fig. 1 through four and the numerical values including the standard deviations of Fig. 1–3 are summarized in Table 1.

In intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes, the baseline bile flow increased almost four times and reached a maximum around 60 minutes and then decreased gradually (Fig. 1. Table 1). Atropine in dosages of 1 and 2 mg reduced the bile flow during cholangiography. The anticholeretic effect of atropine reached a maximum at 60 minutes and lasted for 2½ hours. At 60 minutes, 1 and 2 mg of atropine depressed bile flow −24% ($p < 0.01$) and −16% ($p < 0.05$). No significant difference was found in the anticholeretic effect when both atropine dosages were compared to each other, although the smaller dose reduced bile flow on the average slightly more (Fig. 1, Table I).

One and 2 mg of atropine caused a rise in the iodine concentration in the bile from 45 minutes to the end of the procedure with an average increase compared with baseline of 12 to 16%. While the difference in the bile iodine concentration between baseline and atropine cholangiograms was highest at 90 to 120 minutes (1 mg of atropine +16%, $p < 0.005$ and 2 mg +15%, $p < 0.01$), the peak biliary iodine concentration was obtained with and without atropine at 45 to 60 minutes (Fig. 1). No significant difference in the bile iodine concentration was found between the 1 and 2 mg atropine dosages (Fig. 1, Table I).

Atropine did not enhance the biliary iodine excretion rate, but did cause a slight delay in the increase of the biliary iodipamide excretion in the first 30 minutes when compared with the baseline (Fig.2). The iodipamide excretion rate was similar for baseline and the 2 mg atropine cholangiogram, both reaching a maximum at 60 minutes. However, with the 1 mg atropine dose, a decreased biliary iodipamide excretion rate was found, but compared to baseline the difference was not significant ($p > 0.1$) (Fig. 2, Table I).

No difference was found in the iodipamide serum clearance (Fig. 3) or in the percentage of the infused contrast material excreted in the bile and urine within three hours (Fig. 4) between the baseline and atropine cholangiograms. The bile/urine ratio obtained from the values in Fig. 4 was 1.9 in the baseline study, 1.6 in the 1 mg atropine study and 1.7 in the 2 mg atropine study.

B. *Pipenzolate Bromide* (*PB*). Pipenzolate bromide in a dose of 10 mg produced no significant changes in bile flow or biliary iodipamide concentration. Compared with the effective atropine dosages of 1 and 2 mg the 20 and 40 mg PB doses had similar but overall less marked effects. The 40

TABLE I

Pharmaco-Cholangiography with 0.6 ml/kg Iodipamide and Atropine Sulphate. Mean Values ± 1 Standard Deviation

Minutes after beginning iodipamide infusion	0	15	30	45	60	90	120	150	180
Bile flow (ml/min)									
Baseline	.13 ± .04	.38 ± .08	.41 ± .06	.47 ± .08	.51 ± .08	.50 ± .12	.48 ± .13	.48 ± .12	.43 ± .12
1 mg Atropine	.12 ± .05	.33 ± .15	.36 ± .15	.40 ± .15	.39 ± .12	.40 ± .12	.40 ± .11	.41 ± .11	.44 ± .07
2 mg Atropine	.13 ± .04	.33 ± .13	.37 ± .14	.43 ± .15	.43 ± .15	.44 ± .13	.43 ± .13	.40 ± .11	.42 ± .13
Bile iodine concentration (mg/ml)									
Baseline	0	8.2 ± 3.0	21.3 ± 5.0	22.9 ± 4.7	22.5 ± 4.8	21.4 ± 5.4	21.2 ± 5.2	21.1 ± 4.3	19.4 ± 5.2
1 mg/Atropine	0	5.9 ± 4.1	20.8 ± 3.3	25.6 ± 4.2	25.7 ± 4.5	24.7 ± 3.9	24.5 ± 3.6	23.1 ± 4.5	21.8 ± 4.0
2 mg Atropine	0	6.2 ± 4.3	20.5 ± 4.5	25.5 ± 4.7	25.4 ± 5.1	24.7 ± 5.1	24.0 ± 5.3	23.4 ± 5.1	22.3 ± 5.6
Billiary iodine excretion rate (mg/min)									
Baseline	0	3.1 ± 1.5	8.9 ± 2.7	11.0 ± 3.7	11.5 ± 3.3	10.5 ± 3.2	10.2 ± 3.4	9.9 ± 3.1	8.3 ± 2.7
1 mg Atropine	0	2.2 ± 1.9	7.6 ± 4.1	10.0 ± 4.1	9.7 ± 3.1	9.6 ± 3.3	9.7 ± 2.9	9.4 ± 2.7	9.5 ± 2.0
2 mg Atropine	0	2.4 ± 1.8	7.9 ± 3.9	11.1 ± 4.4	11.4 ± 3.4	10.6 ± 3.5	10.2 ± 32.	9.1 ± 2.3	8.9 ± 1.9
Serum iodine concentration (mg/ml)									
Baseline	0	.74 ± .07	1.04 ± .13	.67 ± .07	.58 ± .06	.43 ± .04	.36 ± .06	.29 ± .06	.24 ± .06
1 mg Atropine	0	.77 ± .12	.99 ± .11	.65 ± .10	.55 ± .06	.45 ± .02	.37 ± .02	.32 ± .03	.28 ± .02
2 mg Atropine	0	.68 ± .04	.97 ± .10	.66 ± .09	.55 ± .05	.43 ± .06	.36 ± .05	.31 ± .05	.26 ± .04

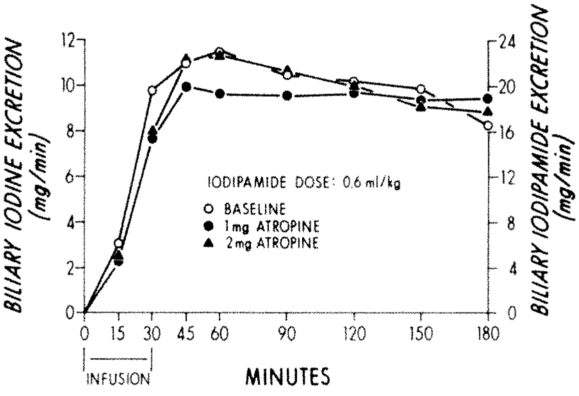

Fig. 2.

Mean biliary iodine and iodipamide excretion rates in six dogs during intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and two different atropine dosages. Standard deviations for each value are given in Table I.

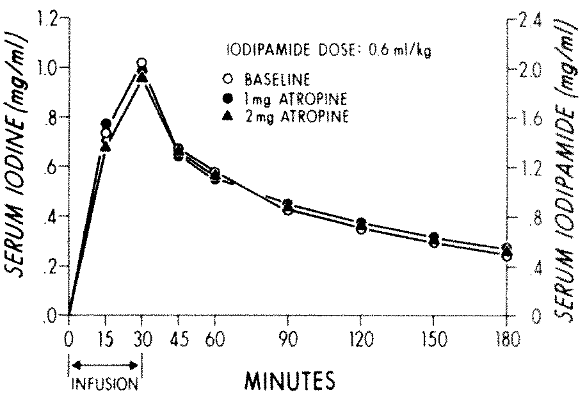

Fig. 3.

Mean serum iodine and iodipamide concentration in six dogs during intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and two different atropine dosages. Standard deviations for each value are given in Table I.

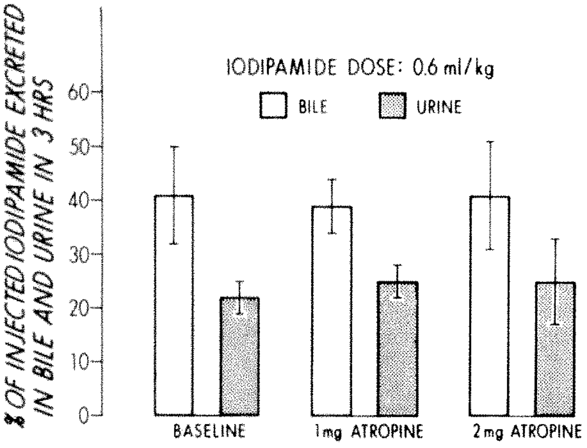

Fig. 4.

Mean iodipamide portion ± 1standard deviation excreted in bile and urine of six dogs in three hours after intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and three different atropine dosages.

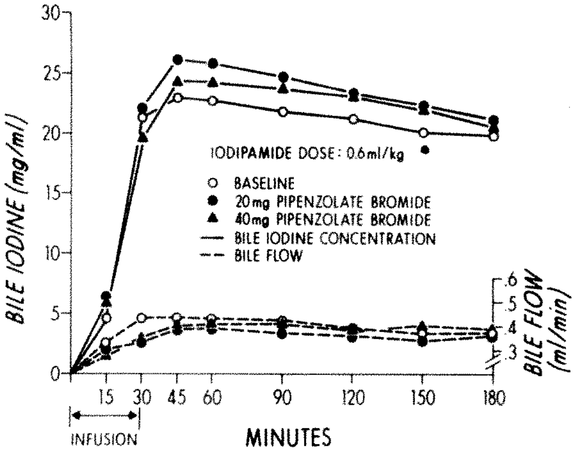

Fig. 5.

Mean bile iodine concentrations and mean bile flow in six dogs during intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and two different pipenzolate bromide dosages. Standard deviations for each value are given in Table II.

TABLE II

Pharmaco-Cholangiography with 0.6 ml/kg Iodipamide and Pipenzolate Bromide. Mean Values ± 1 Standard Deviation

Minutes after beginning iodipamide infusion	0	15	30	45	60	90	120	150	180
Bile flow (ml/min)									
Baseline	.11 ± .03	.33 ± .10	.43 ± .06	.43 ± .04	.43 ± .09	.42 ± .09	.39 ± .06	.37 ± .09	.37 ± .07
20 mg Pipenzolate Bromide	.12 ± 02	.30 ± .04	.33 ± .06	.38 ± .06	.39 ± .08	.37 ± .09	.36 ± .08	.34 ± .07	.36 ± .06
40 mg Pipenzolate Bromide	.10 ± .03	.28 ± .03	.35 ± .04	.40 ± .09	.41 ± .09	.41 ± .10	.39 ± .11	.40 ± .10	.38 ± .10
Bile iodine concentration (mg/ml)									
Baseline	0	4.6 ± 2.1	21.4 ± 4.0	23.0 ± 1.9	22.8 ± 1.5	21.9 ± 1.5	21.3 ± 1.5	20.2 ± 1.6	20.0 ± 1.9
20 mg Pipenzolate Bromide	0	6.4 ± 2.5	22.1 ± 2.7	26.2 ± 2.5	25.9 ± 1.7	24.8 ± 1.9	23.4 ± 2.5	22.4 ± 2.1	21.3 ± 2.6
40 mg Pipenzolate Bromide	0	6.1 ± 2.9	19.4 ± 3.7	24.4 ± 1.4	24.3 ± .9	23.8 ± 1.5	23.2 ± 2.3	22.1 ± 2.9	20.7 ± 3.0
Biliary iodine excretion rate (mg/ml)									
Baseline	0	2.1 ± 1.4	8.6 ± 1.8	9.3 ± 2.1	9.8 ± 1.8	9.2 ± 2.4	8.4 ± 1.8	7.6 ± 2.4	7.4 ± 2.1
20 mg Pipenzolate Bromide	0	2.1 ± 1.1	7.5 ± 2.3	10.1 ± 2.2	10.2 ± 2.5	9.2 ± 2.7	8.6 ± 2.6	7.8 ± 2.3	7.8 ± 2.3
40 mg Pipenzolate Bromide	0	1.8 ± .9	8.2 ± 2.1	9.3 ± 3.1	10.2 ± 2.4	9.8 ± 2.5	9.0 ± 2.4	8.7 ± 2.0	7.9 ± 2.0
Serum iodine concentration (mg/ml)									
Baseline	0	.62 ± .06	.90 ± .16	.63 ± .09	.54 ± .09	.44 ± .07	.37 ± 0.8	.32 ± .06	.29 ± .06
20 mg Pipenzolate Bromide	0	.65 ± .03	.92 ± .09	.64 ± .09	.56 ± .09	.47 ± .06	.40 ± .06	.35 ± .05	.31 ± .05
40 mg Pipenzolate Bromide	0	.63 ± .12	.92 ± .13	.64 ± .10	.54 ± .08	.42 ± .08	.36 ± .07	.31 ± .08	.27 ± .08

mg of PB was on the average slightly less effective than the 20 mg dose. PB decreased the bile production during the first 30 to 60 minutes, the maximum effect being at 30 minutes. At this time, the 20 and 40 mg PB doses diminished bile flow -23% ($p<0.01$) and -19% ($p<0.05$), respectively. Bile iodine concentration with 20 mg PB was maximally increased $+14\%$ ($p<0.05$) at 45 and 60 minutes, when compared with the baseline values. The 40 mg dose maximally increased iodine concentration $+9\%$ ($p<0.1$) between 90 and 150 minutes (Fig. 5, Table II).

The iodipamide excretion rate (Fig. 6), the iodipamide serum clearance (Fig. 7) and the iodipamide bile/urine excretion ratio obtained from the values in Fig. 8 (baseline: 1.4, 20 mg PB, 1.5, and 40 mg PB, 1.4) were not significantly altered by PB.

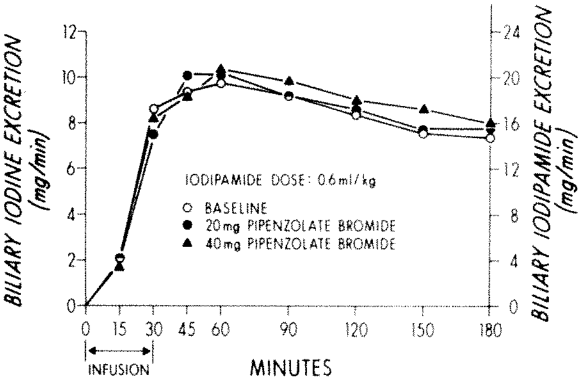

FIG. 6.

Mean biliary iodine and iodipamide excretion rates in six dogs during intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and two different pipenzolate bromide dosages. Standard deviations for each value are given in Table II.

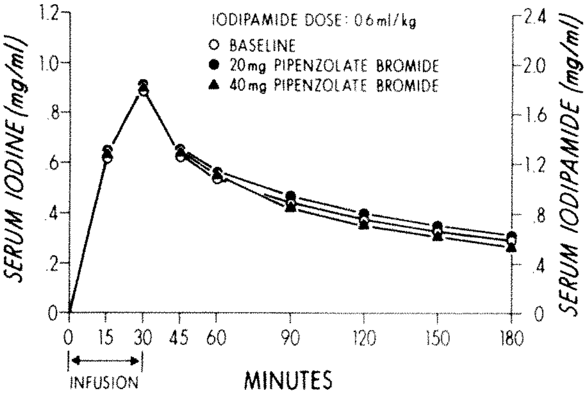

FIG. 7.

Mean serum iodine and iodipamide concentrations in six dogs during intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and two different pipenzolate bromide dosages. Standard deviations for each value are given in Table II.

DISCUSSION

Bile production may be divided into two processes, canalicular and ductular bile formation (Wheeler, 1969). Bile canaliculi lie between the walls of the hepatocytes which form their borders. Excretion of fluid by the hepatocytes into the canaliculi is accordingly called canalicular bile formation. Canaliculi are drained by the smallest intralobar bile ducts, the bile ductules. Fluid production and resorption distal to the canaliculi in the bile ductules and ducts is termed ductular bile formation (Fig. 9).

Iodipamide is excreted from the hepatocytes into the bile canaliculi by an active transport mechanism, the organic anion transport system (Fischer, 1965; Sperber and Sperber, 1971; Erlinger and Dhumeaux, 1974). Active biliary iodipamide excretion is evident from the fact that 1) the biliary transport mechanism is saturable, 2) competitive phenomena between the biliary excretion of iodipamide and other substances such as cholecystographic agents, bromsulphalein (BSP), bilirubin and the glucuronides and sulphuric esters of various substances, exist, and that 3) excretion against a considerable bile/plasma concentration gradient is possible (Sperber and Sperber, 1971). In the dog, the biliary transport maximum (Tm) of iodipamide is about 1·4 mg (0.9 μmol) per minute per kg body weight (Loeb *et al.*, 1975).

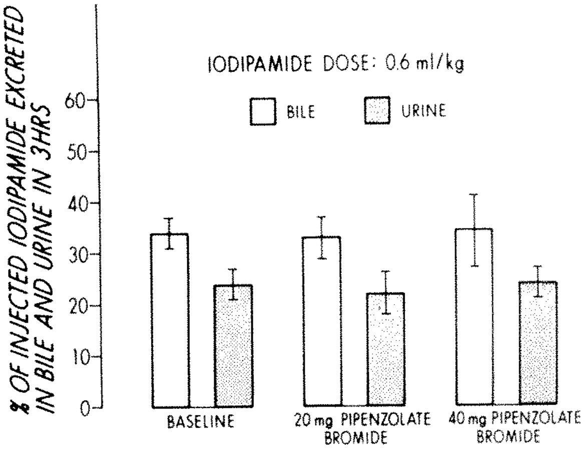

FIG. 8.

Mean iodipamide portion ±1 standard deviation excreted in bile and urine of six dogs in three hours after intravenous cholangiography with 0.6 ml/kg iodipamide infused over 30 minutes and two different pipenzolate bromide dosages.

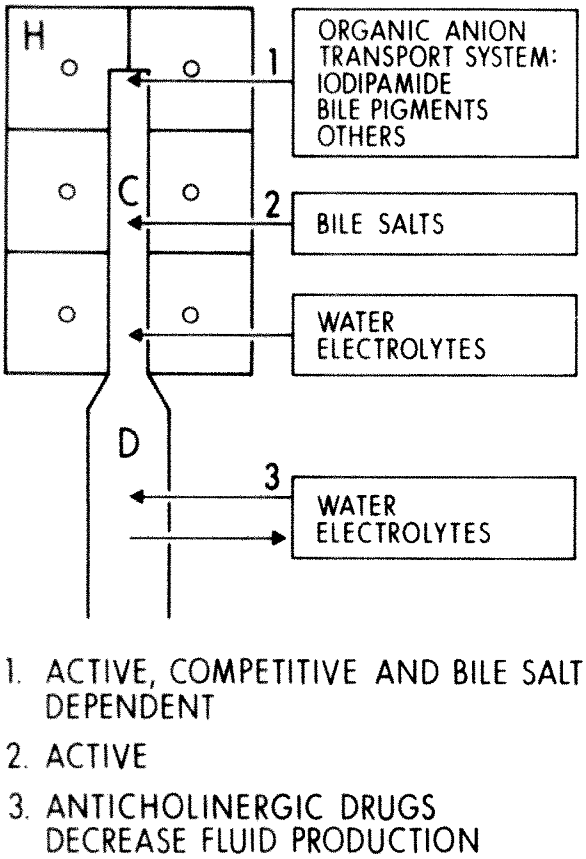
H
C
D
1
2
3
ORGANIC ANION TRANSPORT SYSTEM: IODIPAMIDE BILE PIGMENTS OTHERS
BILE SALTS
WATER ELECTROLYTES
WATER ELECTROLYTES
1. ACTIVE, COMPETITIVE AND BILE SALT DEPENDENT
2. ACTIVE
3. ANTICHOLINERGIC DRUGS DECREASE FLUID PRODUCTION

FIG. 9.

Model summarizing the relevant factors in canalicular and ductular bile formation for the biliary iodipamide excretion. Anticholinergic drugs do not effect the iodipamide excretion rate but increase the bile iodipamide concentration by suppressing the ductular fluid production (H: hepatocyte, C: bile canaliculus, D: bile ductule).

The maximum biliary iodipamide excretion rate is, however, dependent on the bile salts. They are excreted from the hepatocytes into the canaliculi by an active transport system which is independent in the physiologic range from the one excreting iodipamide. The biliary Tm for taurocholate has been shown to be 8.5 μmol per minute per kilogram (11), about ten times that for iodipamide. Bile salts can be considered a major force for bile formation because their secretion provides an osmotic drive for water and electrolytes (Sperber, 1959). The biliary iodipamide excretion rate increased about 20% in the dog by increasing the taurocholate infusion from 0.3 to 0.6 μmol per minute per kilogram and then reached a plateau but no increase in the maximum bile iodine concentration was found (Burgener and Fischer, 1976). A further increase in the taurocholate infusion to 4.8 and 9.6 μmol per kg per minute resulted in a substantial decrease in the biliary iodipamide excretion rate despite further increase in bile flow (Burgener and Fischer, 1976). It appears that when saturation of the biliary Tm for bile salts is approached by unphysiologically high plasma levels, competition between iodipamide and bile salts for the nonspecific biliary organic anion transport mechanism is taking place and results in a depressed biliary iodipamide excretion rate (Fig. 9). Iodipamide itself is known to be a potent choleretic and a recent report suggests that its choleretic effect is canalicular in origin (Feld *et al.*, 1975).

In both the dog and man, secretin, gastrin, histamine, cholinergic drugs and vagal stimulation increase ductular bile fluid production which is limited to the excretion of water and electrolytes (Erlinger and Dhumeaux, 1974). Anticholinergic drugs could, therefore, be expected to reduce the ductular fluid production without affecting the iodipamide excretion rate (Fig. 9). The anticholeretic effect of these drugs might be either direct by vagal blockade or indirect by suppressing the release of hormones which increase bile flow. Indeed, atropine in dosages of 1 and 2 mg, about 0.04 and 0.08 mg per kg reduced bile flow between 10 and 24% in the first $2\frac{1}{2}$ hours during intravenous cholangiography with 0.6 ml/kg iodipamide. The peak effect in suppressing the bile flow was found at 60 minutes. Since this reduction in bile production represents only a small fraction of the choleresis induced by iodipamide, the net bile flow still increased three to four times during intravenous cholangiography with atropine. As could be anticipated, atropine increased the bile iodine concentration proportional to its anticholeretic effect. The bile iodine concentration in the atropine-cholangiograms was from 12 to 16% higher from 45 minutes on when compared with the baseline cholangiograms. As expected, no significant changes were found in the biliary iodipamide excretion rate, the iodipamide serum clearance and the iodipamide bile/urine excretion ratio, when the atropine-cholangiograms were compared with the baseline studies. An increase of the atropine dose from 2 to 4 mg resulted in an almost complete loss of the drug's effect in concentrating the bile iodipamide. The reasons for this observation are unclear but possibly the extrahepatic effects of the large dose outweighed the anticholeretic effects.

Pipenzolate bromide (PB) is a postganglionic parasympathetic inhibitor (Textar, *et al.*, 1955). The drug is used in animal investigations to diminish bile flow variations (Sperber and Sperber, 1971). PB in dosages of 20 and 40 mg 0.75 and 1.5 mg/kg, produced a similar but slightly weaker and shorter lasting effect on bile flow and biliary iodipamide concentration compared to atropine. A significant reduction in bile flow was found with both PB dosages only in the first 60 minutes. The maximum increase in biliary iodine concentration, +14%, occurred with the 20 mg PB dose at 45 and 60 minutes, while the greatest effect of the 40 mg PB dose, +9%, was found between 90 and 150 minutes. As with atropine, no change of the iodipamide excretion rate, the iodipamide serum clearance or the iodipamide bile/urine excretion rate was found.

Since atropine was more effective than PB in enhancing the iodipamide bile concentration in the dog, a clinical trial with the former drug is envisaged to establish its value for cholangiography in the human. It must however be considered that the normal human atropine dose is about three times lower than the dose found effective in the dog in this investigation.

ACKNOWLEDGMENTS

The authors wish to thank P. P. Harnish, B.A., Chief Radiology Laboratory Technologist, for his excellent assistance in the experimental part of the investigation. Our thanks go also to Squibb and Sons, Princetown, New Jersey, for providing us with the iodipamide and to Lakeside Laboratories, Milwaukee, Wisconsin, for providing us with pipezolate bromide.

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Book review

Advances in Cerebral Angiography. Edited by G. Salamon, pp. 375, 1975 (Springer Verlag), DM.59.80.

This book contains 54 contributions originally presented at a meeting devoted to latest advances in cerebral and orbital angiography held in Marseilles in May 1975. The authors are invited experts from the centres in Europe and North America foremost in the field. The contributions are of high standard, some containing mainly original work and some adding to a summary of previously published observations. There are important selections devoted to new apparatus, selective catheterization, magnification, angiotomography, detailed anatomy, comparative anatomy and embryology and embolization.

The editor, Prof. G. Salamon and Springer Verlag are to be congratulated on producing such a well written and beautifully illustrated book with so little delay.

B. E. KENDALL.

1976, *British Journal of Radiology*, *49*, 776–778

Liver volume determination by ultrasound: a feasibility study

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ABSTRACT

The feasibility and precision of an ultrasound method for determining the volume of the liver have been assessed using a Nuclear Enterprises B-scan machine. A relation between estimated liver volume and body weight has been established, showing that liver volume can be determined with a precision of ±195 cm^3 ($P < 0{\cdot}05$).

With the standard non-grey-scale imaging technique employed there is a degree of uncertainty in deciding the liver boundaries, and this constitutes the major source of error.

Routine clinical examination involves an estimation of liver size by means of palpation. However, this technique may yield misleading results in, for example, emphysematous patients, and agreement between ultrasonic and clinical assessment of the position of the lower liver edge relative to the costal margin may be only 50 per cent (Duncan, 1975). Moreover, palpation does not yield a readily quantifiable result which would be of value in following the progress of treatment, such as that of a leukaemic patient receiving a course of chemotherapy.

Although attempts to measure liver volume have been made using radioisotope techniques (Spencer, 1967; Yagan *et al.*, 1962), difficulties in standardizing the liver uptake of the radiopharmaceutical employed have prevented this method being of practical value.

Ultrasound methods have also been used to measure liver volume. For example, Kardel *et al.* (1971) employed a technique involving a series of parallel longitudinal liver scans. Rasmussen (1972) achieved greater accuracy with a more complicated procedure involving radial scanning and computer processing. However, such a method cannot be performed readily with the rectilinear scanning frames of machines possessed by many hospital departments. Moreover, if ultrasound determination of liver volume is to be widely adopted, the method should be comparatively simple.

In the present study, feasibility and precision of an ultrasound method, similar to that originally described by Kardel *et al.* (1971) for determining the volume of the liver, have been assessed. Twelve subjects comprising nine males and three females with no history of hepatic disease were studied.

METHODS

Ultrasound B-scan pictures were obtained using a standard Nuclear Enterprises NE 4101 diasonograph. The scanning-frame of this machine facilitates the imaging of longitudinal or transverse body sections, and allows precise repositioning for serial section scanning.

Investigations were generally performed with a 2·5 MHz transducer, this being substituted by a 1·5 MHz transducer for large subjects. Each scan was photographically recorded on Polaroid 107 film.

The ultrasound investigation involved one transverse scan and a series of longitudinal scans, obtained with the subject lying in the supine position. Imaging of the superior portion of the liver was best achieved with the subject in full inspiration, this being maintained for the duration (about ten seconds) of each scan. Longitudinal changes in liver position between scans, due to body movement or differences in degree of inspiration, were automatically taken into account by the method of estimation employed. However, any lateral movement produced a degree of error which contributed to the overall error observed. The lateral limit of longitudinal scanning was determined by ability to maintain good acoustical contact between probe and patient: this limit was marked on the patient's body. A section through the superior portion of the liver was obtained on the transverse scan, the position of the lateral limit being indicated on the photograph (Fig. 1). The series of longitudinal scans were performed at 1 cm intervals, extending from the body mark to the left extremity of the liver (Fig. 2). In all cases, a compound scanning action was employed to obtain optimum boundary delineation. When required, scans were repeated with appropriate adjustment of the ultrasound parameters.

A longitudinal scan is illustrated in Fig. 3. Liver outlines were traced from the best picture of each longitudinal section, using interpolation methods where necessary. The corresponding enclosed areas were measured with a polar planimeter. A factor

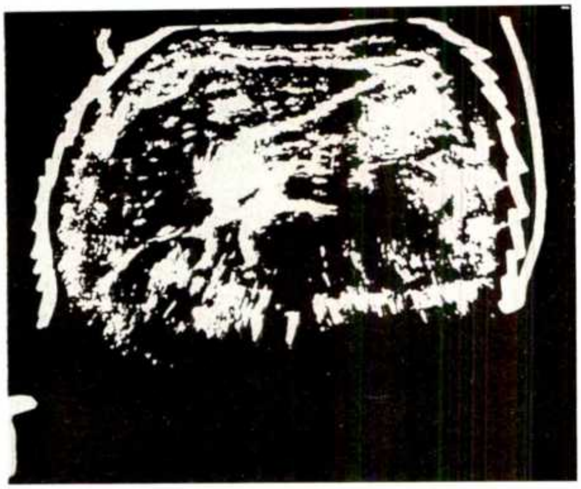

FIG. 1.
Transverse scan showing the lateral limit of longitudinal scanning.

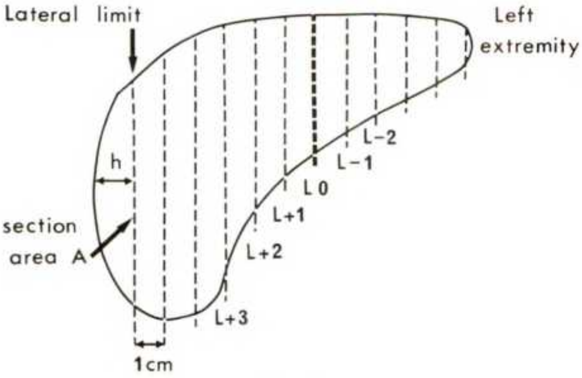

FIG. 2.
Schematic diagram of transverse section of liver, illustrating planes of longitudinal scanning.

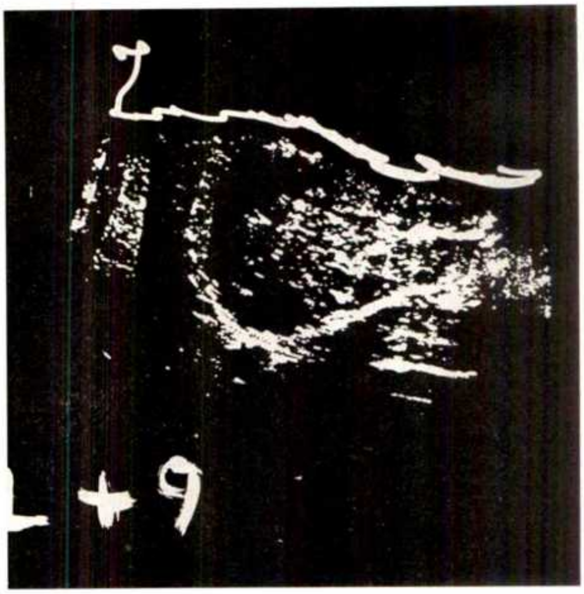

FIG. 3.
Longitudinal scan 9 cm to the right of the sagittal plane.

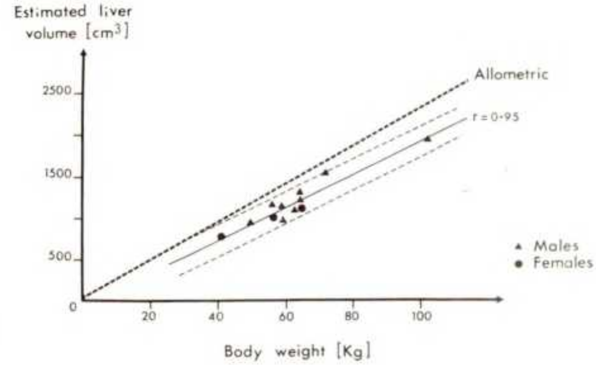

FIG. 4.
Estimated liver volume versus body weight. The solid line is the best linear fit to the experimental data, with ±2 S.E. of estimate indicated by thin dashed lines. A line obeying an allometric equation is also shown (Stahl, 1975).

for converting dimensions measured on the Polaroid film to life size was deduced by observing the separation on film of echoes of known separation produced by an ultrasonic delay line (Hall and Fleming, 1974). Hence, the true area of each liver section was evaluated.

Since the distance between consecutive longitudinal scans was 1 cm, the summation of section areas yielded an estimate of liver volume up to the lateral limit indicated on the transverse scan. The volume (V) of the remaining portion of liver was estimated by assuming that it was equivalent to a paraboloid of base area A and height h, and using the formula: $V = \frac{2}{3} \cdot A \cdot h$. The area A was that of the first longitudinal section, and the height h was measured from the transverse scan (Fig. 2). Hence, total liver volume was calculated.

RESULTS

For each of the 12 subjects studied, liver volume was estimated from the scans by two independent observers. Good agreement between observers was found, discrepancies averaging 9·4 per cent of the means. This value reflects the subjective error of observers in identifying the liver outline on the Polaroid photographs. The algebraic mean discrepancy was less than 1 per cent, indicating the lack of significant systematic error of estimation by either observer.

Estimated liver volume was considered in relation to bodyweight (Fig. 4). Good linear correlation was demonstrated ($r = 0{\cdot}95$), with the standard error of the estimate equalling 97·5 cm^3. Thus, an individual whose estimated liver volume differs from the predicted value by more than 195 cm^3 (2 × S.E. of estimate) can be said, with 95 per cent degree of confidence, to be abnormal. This implies that the liver volume of, for example, a subject weighing 70 kG can be assessed to within ±15 per cent precision ($P < 0{\cdot}05$). Figure 4 includes a line obeying an allometric equation $L = aW^b$ derived from post-mortem measurement of liver size in primates (Stahl, 1965), and relating liver size L to bodyweight W, with a and b constants. This can be seen to yield slightly higher estimates of liver volume than our experimentally determined relation. However, when uncertainty in the allometric equation is considered, the difference is not significant.

Repeat ultrasonic investigations of six subjects were conducted, and liver volume was again assessed by two observers. Values obtained by each observer were compared with the corresponding results of the first examinations. Reasonably good agreement was achieved, discrepancies between repeat assessment averaging 14·9 per cent for the first observer and 12·3 per cent for the second. This shows that the principal source of error is experimental rather than due to biological variation. Thus, change in liver volume in any individual cannot be assessed with greater precision than the initial estimation of abnormality.

Discussion

A relation between ultrasonically estimated liver volume and bodyweight has been established. Volume can be determined to within ±195 cm^3 precision with 95 per cent confidence. Since future evaluation of the clinical significance of estimated liver volume would be with reference to our calibration relation, repeatability of the method is more important than its absolute accuracy. Thus, the fact that our relation differs somewhat from the allometric equation of Stahl (1965) is of little consequence. Indeed, attempted standardization of the ultrasound method, by comparison with liver volume as measured at post-mortem, is likely to be misleading due to post-mortem changes resulting from cessation of blood flow, etc.

A criticism of current ultrasound determinations of organ volume is inherent in the degree of uncertainty in deciding section boundaries; our duplicate assessments indicate that this is the main source of error. The lack of complete outline is due to the difficulty of obtaining normal incidence of the ultrasound beam at all parts of the organ boundary. However, the problem may be alleviated by the use of grey-scale imaging techniques (Taylor *et al.*, 1973; Railton and Hall, 1975). In these, the parenchyma of the organ is imaged by diffuse scattering in addition to obtaining the boundaries as in the non-grey scale method.

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The application of a digital whole body scanner to the dosimetry of intralymphatic ^{32}P/^{131}I Lipiodol

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ABSTRACT

A quantitative, digital-output, whole-body scanner in a low background area has been used in the dosimetry of ^{32}P/^{131}I Lipiodol for intralymphatic radiotherapy.

Five patients with malignant melanoma received intralymphatic administrations of Lipiodol labelled with 6 mCi ^{32}P and 1.5 mCi ^{131}I. The ^{131}I is used primarily as a tracer for external measurements and the ^{32}P as the chief therapeutic agent. Whole body scans were made at intervals for up to 15 days using the digital scanner, with the spectrometer set over the 364 keV photopeak of ^{131}I. On the same occasions complete gamma-spectra were obtained for these patients using a 2 m arc, single detector whole body counter. The method used in estimating the activity at various sites in the body from the digital whole body scans is described and problems that arise in using ^{131}I as a tracer for ^{32}P Lipiodol in this work are discussed.

For the administered activities mentioned above, maximum absorbed doses to the lymph nodes were found to range from 30–96 krad with a mean value of 51 krad. Uptake of radioactivity was also found in the lungs, resulting in absorbed doses of 350–960 rad with a mean value of 540 rad.

One approach to the treatment of malignant melanoma has been the intralymphatic injection of radioactive colloids following wide surgical excision of the primary melanoma, in order to sterilize its lymphatic drainage. Jantet (1962) used ^{198}Au colloid, and, after an injection of between 20 and 60 mCi into the lower limb, external counting showed that activity was localized at the sites of the lymph nodes and also distributed over a wide area, with some activity in the liver and spleen. Absorbed doses to nodes were estimated from some data on the activity found in dissected nodes, combined with results of *in vivo* counting. The results varied widely between patients and from the values cited an activity of 20 mCi injected in the lower limb could produce absorbed doses in the range 9–70 krad.

Buraggi *et al.* (1963) introduced the use of ^{131}I Lipiodol for intralymphatic therapy with activities of 10–15 mCi. A single detector *in vivo* counter method was used in estimating activity localized at specific sites while dimensions of nodes were estimated from contrast radiographs. The mean value of absorbed dose for 39 patients was 842 rad per mCi injected with a range of 125 to 3676 rad. No mention was made of activity being found in the lungs nor of the volume of Lipiodol injected.

Edwards (1969) used ^{131}I Lipiodol and found the results encouraging but stressed the need for a full clinical trial. He administered 40–45 mCi ^{131}I in 4 ml Lipiodol for the lower limb and 30–35 mCi ^{131}I in 2 ml for the upper limb; he reported that activity spread to the lungs, the quantity appearing to increase with the volume injected. It was estimated by external counting that an average of about 12% of the administered activity spread to the lungs. In successful administrations the concentration of ^{131}I in the blood was about 0.01% of the administered activity per litre and average excretion in urine was some 1% of the administered activity in 24 hours. It appears that the estimated doses to the nodes were up to 100 krad (stated in the text to be "100,000 rads per gm. tissue").

Owen *et al.* (1969) reported a dosimetry study on 13 patients who had therapeutic doses of ^{131}I Lipiodol, with wide ranges of doses to lungs and nodes. They recommended the use of ^{32}P for intralymphatic therapy.

Pfannenstiel *et al.* (1969a) and Pfannenstiel *et al.* (1969b) made dosimetry studies of ^{131}I Lipiodol. Their results were derived from a combination of scanning and profile counting. They reported a mean absorbed dose to the lymph nodes of 5000 rad per mCi administered, assuming a total mass of 19.2g. They also reported finding 4.6% of the activity in the lungs. Results for ^{131}I/^{32}P administrations to eight patients with Hodgkin's disease and metastases involving the retroperitoneal lymph nodes were also referred to but no details were given of the methods of analysis used.

Dosimetry studies of ^{131}I Lipiodol at this hospital using a static collimated detector for *in vivo* measurements have been reported (Eversden *et al.*, 1968): the inadequacy of this method was realized at the time and provided one incentive to the development of a new dual head automatic scanning system with digital output.

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In the present study, estimates of absorbed dose are presented for five female patients, aged between 32 and 77 years, who have all had a malignant melanoma on the lower limb excised.

MATERIALS AND METHODS

^{32}P/^{131}I Lipiodol was obtained from Sorin (Italy) (LIP-32-B). The compound was injected intralymphatically into the foot of the affected limb. The activity of each sample was usually 6 mCi ^{32}P and 1.5 mCi ^{131}I, the radioiodine being used for localization and not primarily for therapy. The patients were premedicated with Lugol's iodine 24 hours before the injection and the medication continued for a week afterwards in order to reduce the uptake of ^{131}I in the thyroid. Lymphograms and photoscans were taken in the X-ray and Nuclear Medicine Departments respectively. Whole body retention measurements and serial whole body scans were carried out in the low background laboratory.

(a) *Whole Body Retention*

A two metre arc, single NaI (Tl) detector whole body counter linked to a multichannel analyser was used to read counts from patients at intervals over a period of two weeks; corrections for physical decay and instrumental variations were made using standards of ^{32}P and ^{131}I measured on each occasion. These data were analysed to provide estimates of the retention (defined as the percentage of administered activity, corrected for physical decay) of the two radionuclides as follows:

Contributions to the count rates for ^{131}I and ^{32}P in the two energy bands 70–170 keV (Channel A) and 170–440 keV (Channel B) were separately determined, and the ratio

$$R = \frac{\text{counts rate in Channel A}}{\text{count rate in Channel B}}$$

was calculated for each radionuclide.

For ^{32}P the ratio was found by using measurements on a patient who had been injected with ^{32}P Lipiodol alone for treatment; the value of R obtained was four. For ^{131}I the ratio was found by two different methods: (a) using measurements on two patients under treatment with ^{131}I for thyroid carcinoma, but in whom the radioactivity was distributed throughout the body as the thyroid had been ablated, and (b) using a small source of ^{131}I at various depths in a 20 cm thick block of tissue-equivalent rubber. For the thyroid patients the values of the ratio R were 0.8 and 0.9, while for the small ^{131}I source at depths from 2 to 10 cm the value of R ranged from 0.9 to 1.1. A value of 0.8 was assumed for this ratio; the effect of errors in this quantity is discussed below.

(b) *Uptake in Organs*

The dual detector whole body scanner has been described by Cottrall *et al.* (1973) and its use for sequential scanning reported by Trott *et al.* (1973). For this study, 25 hole lead collimators were used; the scan length was 176 cm and the area was scanned in a series of nine lines. Counts in the 170–440 keV band were recorded at intervals of 4 cm and the scan speed was 0.8 cm sec^{-1}.

The scanner was first calibrated using cylinders of water containing ^{131}I to simulate the nodes and the lungs. Cylinders of different sizes from 0.25 to 1300 ml were placed between slabs of tissue-equivalent rubber and scanned as described above. From these experiments the variation of calibration factor (defined as the total net count recorded for 1 μCi ^{131}I in the whole container) with container size was determined. It was found that within the 10% contour and the source sizes shown in Table I there was very little variation in the calibration factor for volumes of 7 ml upwards. For smaller sources there was a significant variation as the source was displaced relative to the actual line of the scan. The mean calibration factor averaged over all sources was 123 counts μCi^{-1} for the 10% contour, which gave the closest correspondence with the physical sizes of the larger sources tested.

For each scan of a patient a numerical array was obtained which gave the total counts at each matrix point. Computer programs were used to provide displays including isocount lines (*e.g.* Fig. 1) and symbolic presentations (Trott *et al.*, 1975). However, the analysis on which dosimetry was based was carried out manually using the numerical data corrected for background.

The digital scans showed that the highest concentration of radioactivity was (as intended) in the lymphatic chain in the pelvis. Lymphograms (*e.g.* Fig. 2) normally showed that the chain of nodes retaining the Lipiodol extended to just below the level of the lower costal margin. Photoscans of chest and pelvis (*e.g.* Fig. 3) confirmed the high uptake in the pelvic nodes compared with that in the lungs in all patients. Anatomical landmarks were superimposed on the digital scans and a line was drawn corresponding to the level of the lower costal margin dividing the data into two areas. Counts in the area above this line were taken to be due to activity in the lungs and counts below the line were regarded as being due to activity in the lymphatic chain. The two areas were treated separately.

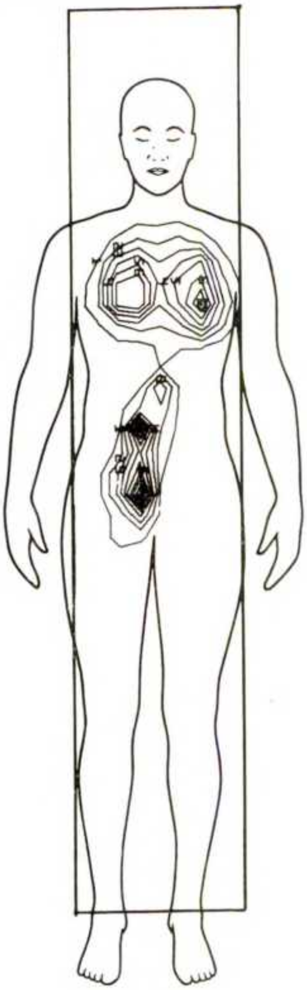

FIG. 1.
Isocount display at three hours for patient 72/43. Conditions as described in text.

To estimate activity in the pelvic nodes the maximum count in the pelvic area was first identified. The total of all counts with a value greater than or equal to 10% of the maximum value was summed. A similar analysis was made for other contour levels. The radioactivity due to ^{131}I was then estimated using the relevant calibration factor from Table I (*i.e.* 123 counts μCi^{-1} for the 10% contour).

Activity in the lungs was found in the same way from the summed counts in the area between the costal margin and the level of the supra-sternal notch. Radioactivity in the right and left lungs could not be separately estimated by this method.

The above procedure was used for sequential scans in order to assess the time integral of ^{131}I activity in lungs and nodes. Activity due to ^{32}P was found by multiplying results for ^{131}I by the ratio of the injected activities, assuming that both radionuclides have the same biological clearance. The validity of this assumption is discussed below.

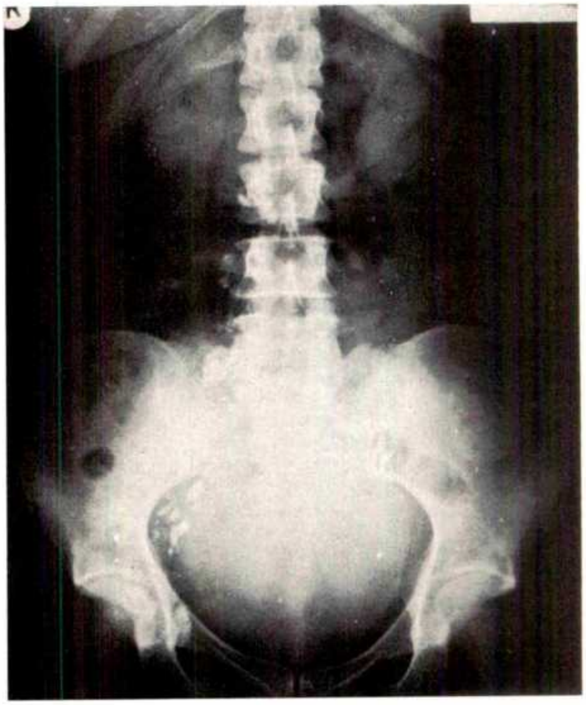

FIG. 2.
Lymphogram at 24 hours for patient 72/43.

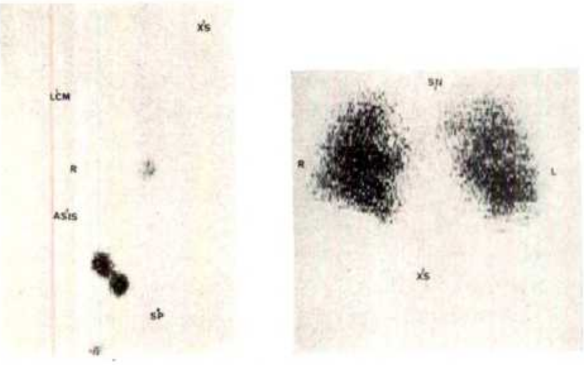

FIG. 3.
Photoscans of chest (right) and pelvis (left) at 24 hours for patient 72/43.

(c) *Activity in Blood and Urine*

For two patients urine was collected for 48 hours and blood samples were obtained on alternate days over two weeks after the administration of Lipiodol.

TABLE I

EXPERIMENTAL STUDIES WITH WHOLE BODY SCANNER: VARIATION WITH CONTOUR LEVEL AND SOURCE SIZE OF TOTAL COUNT (CORRECTED FOR BACKGROUND) PER μCi ^{131}I

Source Volume (ml)	Σ10%	E20%	Σ30%	Comments
0.25	165	165	165	On scan line
	138	121	121	0.5 cm from line
	98	72	72	1 cm from line
	108	108	97	2 cm from line
1	145	135	135	On scan line
	130	122	109	0.5 cm from line
	95	95	95	1 cm from line
	114	114	86	2 cm from line
7	135	120	120	In centre of area
13	142	115	115	In centre of area
28	130	114	114	In centre of area
60	116	104	104	In centre of area
120	135	121	121	In centre of area
300	110	95	88	In centre of area
650	109	94	76	In centre of area
650	107	103	80	*
650	115	102	91	
1300	116	113	107	In centre of area
Mean	123	112	105	

*Net counts over individual source when there is a second source of the same size 15 cm away.

Σx% indicates sum of all counts with value greater than x% of maximum count recorded in scan.

Scan area 176 cm × 32 cm in 9 lines with 4 cm spacing.

Energy band for ^{131}I 170–440 keV.

Scanning speed 0.8 cm s^{-1}.

TABLE II

THREE HOUR UPTAKE OF ACTIVITY IN LUNGS AND NODES: THREE DIFFERENT CONTOUR LEVELS USED

Patient and administered activity	Site	% administered activity		
		10%	20%*	30%†
72/43 (4.8 mCi ^{32}P; 1.25 mCi ^{131}I)	Nodes	28	26	24
	Lungs	56	56	53
72/44 (5.1 mCi ^{32}P; 1.33 mCi ^{131}I)	Nodes	63	61	63
	Lungs	15	16	16
	*SCN	1	—	—
73/25 (5.7 mCi ^{32}P; 1.5 mCi ^{131}I)	Nodes	39	38	29
	Lungs	30	28	26
73/30 (5.4 mCi ^{32}P; 0.4 mCi ^{131}I)	Nodes	53	44	42
	Lungs	21	22	20
73/64 (4.2 mCi ^{32}P; 1.0 mCi ^{131}I)	Nodes	29	28	24
	Lungs	50	48	45

*Supraclavicular node (see Text).

†Contour levels.

Activity in urine was measured in a ring of 16 G.M. tubes and aliquots of whole blood and plasma were assayed in an auto-gamma well type scintillation counter.

RESULTS OF MEASUREMENTS ON PATIENTS

(a) *Whole Body Retention*

Using the ratios referred to above, the fractional activities of ^{32}P and ^{131}I retained were separately estimated from the whole body spectra over periods of about 15 days (as illustrated in Fig. 4). The results indicate that, bearing in mind the poor counting statistics for ^{32}P, it is reasonable to assume in the dosimetry that the two radionuclides are cleared from the body at the same rate. For patient 73/30 the ^{32}P appeared to be cleared much more slowly than the ^{131}I; the iodine fraction in the administered Lipiodol for this patient was only about a quarter of that requested resulting in very low count rates and therefore considerable errors in Channel B.

There are two indications that the ratio R (defined above) may be nearer to 1.0 than to 0.8 (the value observed for the ^{131}I patients), namely the measurements with the small source in tissue-equivalent rubber and the calibration factor (counts sec^{-1} mCi^{-1} in the 70–170 keV energy band) obtained from the patient who had ^{32}P alone. Trials with R=1 gave a biological half life of ^{32}P longer than that of ^{131}I but there was a greater statistical fluctuation in the values for the fraction of ^{32}P retained. The effect on the absorbed dose calculations of assuming the greater half life for ^{32}P is discussed below.

(b) *Distribution*

As discussed above, net counts were tabulated for all areas showing significant uptake, these being identified as arising from activity in either lungs or nodes. Results for the initial uptake in lungs and nodes are shown in Table II. Estimates of activity have been made using three different contour levels together with the appropriate calibration factors given in Table I.

The isocount displays were adjusted to record counts down to 10% of the maximum count recorded in the whole scan. However, it is necessary in making computations to refer back to the original data since otherwise regions of significant uptake may be eliminated. This can be seen by examining Fig. 5, the numerical data for patient 72/44. Here there was significant activity in the lungs and also in a supraclavicular node on the left side, but these nevertheless were below 10% of the maximum observed count rate and so were not shown at all on the

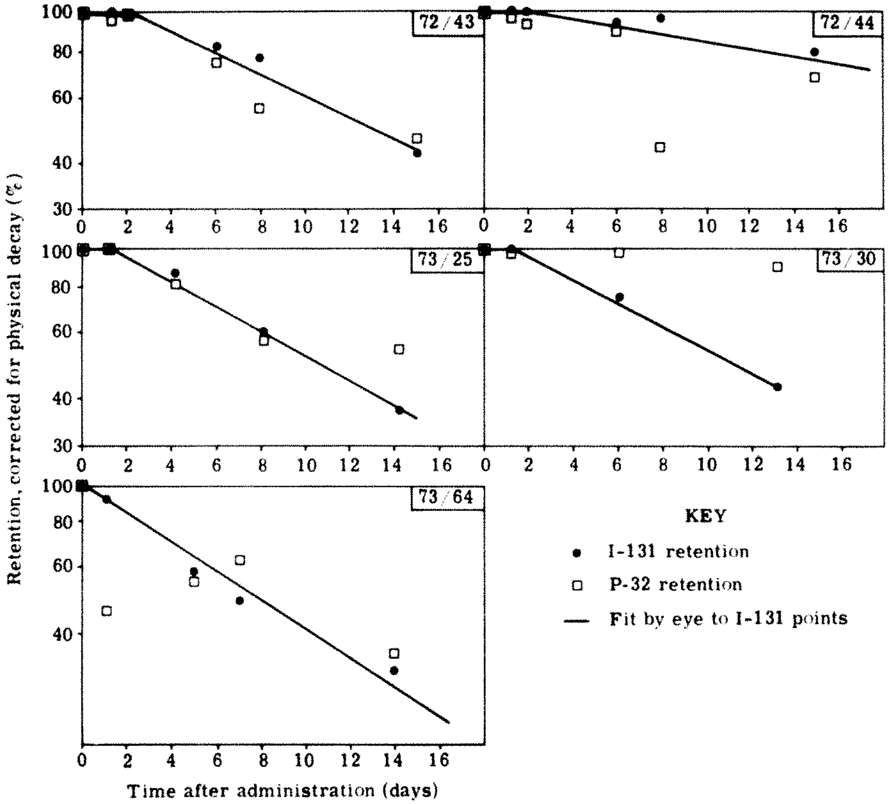

FIG. 4.

Whole body retention of ^{32}P and ^{131}I. Results for two metre arc single detector whole body counter. Energy bands: 70–170 keV for ^{32}P, 170–440 keV for ^{131}I. Corrections made for contribution of ^{131}I to the lower energy band and of ^{32}P to the upper energy band as described in text.

isocount displays. The single node did in fact appear on the photoscan of the chest.

No activity could be detected in the thyroid gland in any of the patients.

(c) *Blood and Urine*

Activity in blood and urine for two patients indicated that leakage into the general circulation was negligible. For patient 72/43 about 2% of the administered activity was present in the urine during the first 48 hours and peak activity in the blood occurred at eight days corresponding to 0.15% administered activity/litre plasma. For patient 72/44, 48 hours' urine contained 1.5% administered activity and peak activity in the blood occurred at six days corresponding to 0.07% administered activity/litre plasma. Figure 6 shows the variation in concentration of ^{131}I in the blood for these patients.

ABSORBED DOSE CALCULATION

Absorbed dose calculations were based on the formulation of Loevinger and Berman (1968):

$$D(t \longleftarrow s) = \frac{\tilde{A}\,\psi\,\Delta}{m}$$

where t = target
s = source
$\tilde{A}$ = cumulated (time integral) activity in source
Δ = energy emitted per transformation
ψ = absorbed fraction
m = mass of target.

Data for the energy emitted Δ and the absorbed fraction were obtained from M.I.R.D. pamphlets based on the work of Dillman (1969) and Snyder *et al.*, (1969). Table III summarizes the radionuclide data.

The absorbed doses to the lungs and nodes are given in Table IV for the five patients studied; three contour levels were used in the initial analysis but only the 10% contour for the final estimates. The calculations assume that the radionuclides are distributed uniformly throughout the tissues involved.

41	49	103	173	366	1476	156	80	63	Supraclavicular node
63	168	304	294	967	935	394	129	68	
85	317	571	629	519	658	694	253	81	
127	565	811	748	433	1020	1043	325	84	
162	712	1055	878	463	899	1117	347	98	Lung maximum•
144	419	736	627	366	607	1001	253	79	
139	226	317	342	359	372	328	170	45	Level of lower costal margin
113	217	403	614	989	376	224	157	40	
118	338	569	3232	2409	526	264	147	54	
210	504	915	4991	1759	570	332	175	48	
284	731	1361	9798	2177	684	329	195	96	
442	1050	2440	10079	1740	667	371	191	95	
570	1342	9669	9686	1538	637	364	200	91	
588	1439	15083	4057	1269	543	321	185	110	Lymphatic chain maximum
513	1241	11319	2815	916	435	258	174	106	
367	873	9757	980	563	303	197	140	83	
266	403	814	477	245	206	173	120	62	
170	216	328	248	160	123	102	70	25	

FIG. 5.

Part of net count array at three hours for patient 72/44. Area shown is from sternal notch to symphysis pubis. The highest counts found for sites of lymph nodes and lungs are indicated.

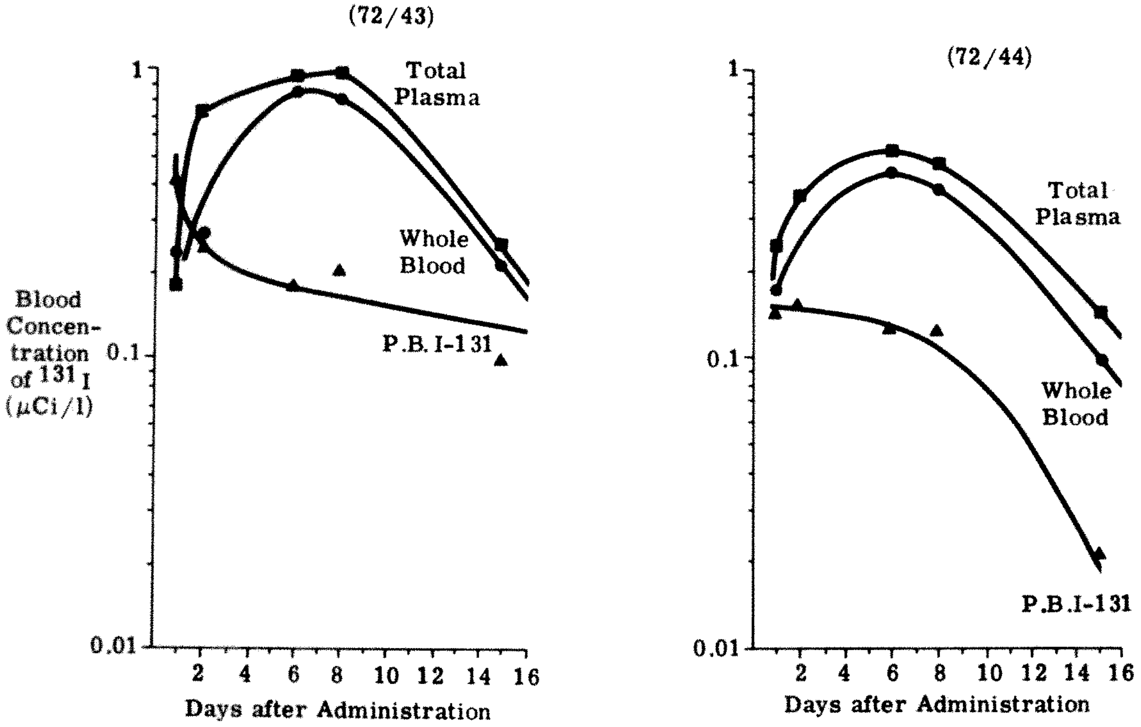

FIG. 6.

Concentration of ^{131}I activity in the blood for patients 72/43 and 72/44.

For the lungs, a standard mass of 999g has been assumed (Snyder *et al.*, 1969). For patients 73/25 and 73/30 the lung clearance was not initially exponential. The activity for 73/25 reached a peak at four days after the administration of the dose and for 73/30 peak lung activity occurred after one day. In both cases the clearance was exponential thereafter with half lives quoted in Table IV. In order to find the dose to the lungs the activity-time curves were integrated graphically.

Sizes of nodes were estimated using a method similar to that of Pfannenstiel *et al.* (1969a). *i.e.* the nodes were treated as ellipsoids whose axes were determined from the 24 hour antero-posterior lymphograms. The depth of the ellipsoid was taken to be the same as its breadth. Correction was made for the magnification on the X-ray films. This analysis was carried out for all the nodes retaining lipiodol; the total mass of the lymph nodes was calculated taking a density of 1.2 g cm^{-3} to allow for the presence of the Lipiodol (see Table IV).

Our studies show that if the activities of $^{32}P/^{131}I$ injected are in the ratio of 6:1.5 then the absorbed dose to the lungs due to ^{131}I, used only for localization, is about 5% of that due to ^{32}P. For the same ratio of activities the dose to a chain of nodes due to ^{131}I does not exceed 10% of the ^{32}P dose.

The accuracy of the estimates of absorbed dose was considerably reduced on one occasion (not included in these estimates) when only ^{32}P labelled Lipiodol was available. Photoscans were difficult to obtain because the count rate was so low, and in order to perform digital whole body scans coarser collimation had to be used, together with a line spacing of 8 cm.

TABLE III

RADIONUCLIDE DATA FOR DOSIMETRY

		Energy emitted per nuclear transformation g rad μci^{-1}	
Radionuclide	Half-life (days)	$\Sigma\Delta$* non pen	$\Sigma\Delta$† pen
^{32}P	14.3	1.480	
^{131}I	8.05	0.414	0.804

*non-penetrating $\Sigma\Delta$ for all β-rays, internal conversion electrons, Auger electrons, X and $\gamma < 0.015$ MeV. Bremsstrahlung not included.

†penetrating $\Sigma\Delta$ for all X and $\gamma > 0.015$ MeV. Bremsstrahlung not included.

DISCUSSION

The assumptions made in deriving the estimates of absorbed dose given in Table IV need examination.

First, it has been assumed that the beta particle energy is totally absorbed. While this is reasonable for the lungs, for the nodes a range of absorbed doses can be calculated corresponding to the range of radii of nodes in the chain. The radius of a node (assuming spherical geometry) was found to have a mean value of 4 mm with a range of 1 to 10 mm. Maximum

TABLE IV

ESTIMATES OF ABSORBED DOSE (β and γ) FOR 3 DIFFERENT CONTOUR LEVELS

				^{32}P			^{131}I						
				non-penetrating (krad)			non-penetrating (krad)			penetrating (rad)			Total absorbed dose (krad)
Patient	Site	Mass	T$_{\frac{1}{2}}$ biol. (days)	*10%	20%	30%	10%	20%	30%	10%	20%	30%	10%
72/43	Nodes	23	18.6	24.6	22.2	20.3	1.2	1.1	1.0	72	65	59	26
	Lungs	999	12	0.90	0.90	0.83	0.05	0.05	0.05	5	5	5	0.96
72/44	Nodes	33	21	42.1	40.7	41.9	2.1	2.0	2.1	123	119	127	44
	Lungs	999	20	0.33	0.34	0.34	0.02	0.02	0.02	2	2	2	0.35
73/25	Nodes	15	15	55.3	54.0	41.8	2.9	2.8	2.2	169	165	127	58
	Lungs	999	3.5	0.50	0.46	0.42	0.02	0.02	0.02	2	2	2	0.52
73/30	Nodes	16	36	94.2	77.3	74.4	1.2	1.0	0.9	70	57	55	96
	Lungs	999	8	0.45	0.47	0.44	0.01	0.01	0.01	1	1	1	0.46
73/64	Nodes	17	17	28.8	27.1	23.4	1.3	1.2	1.1	78	74	64	30
	Lungs	999	4.7	0.38	0.36	0.33	0.02	0.02	0.02	2	2	2	0.40

*The values taken for $\bar{A}$ and so the values of absorbed dose depend upon the contour levels used (Tables I and II). Results for three different contour levels are shown for individual contributions and for one contour for the total.

ranges of β-particles in tissue for ^{32}P and ^{131}I are 7 mm and 2 mm respectively. Loevinger *et al.* (1956) have shown that the absorbed fraction for a 1 mm radius sphere is 0.9 for ^{131}I and 0.3 for ^{32}P; for a sphere of radius 4 mm the fractions are 1.0 and 0.8 for ^{131}I and ^{32}P respectively. In this respect, therefore, the values cited in Table IV may overestimate the doses to nodes.

Second, there is some evidence from the whole body retention data that the biological half-life of ^{32}P may be longer than that of ^{131}I. For the nodes, the effect on the calculated doses of assuming in the extreme case no clearance of ^{32}P can be readily calculated using the data in Table IV. For example, for patient 73/25 with the shortest biological half-life in the series, the absorbed dose due to ^{32}P would be approximately doubled. For the lungs, however, Table IV shows a biological half-life based on ^{131}I retention generally much shorter than for the nodes, and it would be unrealistic to assume no clearance at all for the ^{32}P. It is evident, nevertheless, that the lung doses will not be less than the values quoted.

It is clearly desirable, in order to permit calculations of the half-lives of both ^{32}P and ^{131}I in the nodes and lungs, to be able to record simultaneously in the two energy bands during scanning. However, it was not possible to do this with the equipment available at the time and it was not felt justifiable to scan the patient twice on each visit. Apparatus is now available which makes it possible to collect counts from two channels while in multi-scalar mode; any future patients receiving this form of treatment will therefore be scanned on the new system and this problem will be overcome.

Finally, estimates of the dimensions of the nodes also have a considerable influence on the values obtained for the absorbed dose received by the nodes; in consequence, these values are likely to be again less accurate than those for the dose to the lungs. However, for the radiotherapist planning any subsequent treatment to this site, it is the dose already received by the lungs which is of particular importance.

Comparisons of the results of this study with those of Pfannenstiel *et al.* (1969a and b) are given in Table V. We have not been able to identify the primary cause of the large discrepancy for the absorbed dose to the nodes between the findings of these authors and ourselves: the masses assumed are the same and the results for fraction retained and rates for clearance are similar. However, the existence of such a discrepancy indicates that perhaps the biological clearance is not as simple as at first assumed, and also serves to underline the need for detailed comparative studies at different institutions when such exploratory forms of therapy are being attempted.

TABLE V

Comparison of intralymphatic dosimetry studies using in vivo counting techniques

	Pfannenstiel *et al.* (1969)	Royal Marsden Hospital (1973)
Number of patients in study	8	5
Diagnosis	Hodgkin's Disease	Malignant melanoma
Administered activity		
^{32}P	4 mCi	6 mCi
^{131}I	2 mCi	1.5 mCi
Total mass of nodes:		
Mean	22 g	21 g
range	5–53 g	15–33 g
Absorbed dose to nodes:		
Mean	217 krad	51 krad
range	45–495 krad	30–96 krad
Absorbed dose to lungs:		
Mean	250 rad	540 rad
range	120–790 rad	350–960 rad

In both studies a lung mass of 1 kg was assumed for all patients.

Acknowledgments

The patients reported here were all under the care of Dr. R. L. Morgan, and the lymphography was done by Dr. J. S. Macdonald.

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Book review

Radiology of Bone Diseases. By G. B. Greenfield, M.D., 2nd edn., pp. xvi+667, 1975. (Philadelphia and Toronto, J. P. Lippencott Co., distributed in the U.K. by Blackwell Scientific Publications), £27·50.

For the second edition of his work, Professor Greenfield has added fresh constituents to an already established and successful formula. Recent advances in metabolic bone disease and bone dysplasias have been included. There is now a new section on "Disorders of the Joints".

Disease entities are grouped according to their essential radiographic features and are illuminated throughout by an eminently practical approach to problem solving. The text is written with great economy and much emphasis is placed in the use of tabulated data. This is a distinctive feature which may affect readers in different ways. In addition to conventional disease classifications, there are lists of the causes of specific radiological signs, differential diagnosis and disease associations with characteristic X-ray appearances. The formidable size of some of these tables may at first sight appear rather daunting to the tyro who may not always be in a position to appreciate the frequency or significance of individual features. The availability of these checklists will undoubtedly save students considerable time and effort in preparation for examinations. On many occasions, however, it is this very act of compilation from individual research and reading which will ensure the deepest impression on the memory. The reader of course, can have the best of both worlds with this book.

The minor syndromes of dwarfism are neatly summarized and presented in a manner which highlights the characteristic and distinguishing features. Although this is only a small part of the book, it does illustrate the author's concern for the reader who might be faced with a difficult diagnostic bone problem in unfamiliar circumstances. There are comprehensive cross-references which are most helpful, but occasionally this predisposes to omissions. For example, the same description of vertebral involvement in Hodgkin's Disease is given in three different contexts to emphasize differential diagnosis. There is, however, no specific consideration given to the other types of bone lesion found in this not uncommon disorder.

Over 1,200 illustrations are included and these have been carefully selected to show maximum detail. There is a comprehensive bibliography at the end of each chapter with British publications well represented. This is particularly useful since papers relating to skeletal disease can appear in diverse journals of pathology, paediatrics, orthopaedics, rheumatology as well as those of general medicine and radiology.

This book makes a valuable contribution to the field of musculoskeletal disease and is well worthy of a place in the radiological library.

W. M. PARK.

1976, *British Journal of Radiology*, *49*, 788–793

The analysis of radioisotope brain scans by comparison with normal patterns of uptake

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ABSTRACT

A previously described method for the computer analysis of radioisotope brain scans has been further developed. A patient scan is matched with a series of "normal" scans to find the closest fit and the "normal" scan is then subtracted from the patient scan. The results are displayed in terms of the standard deviation from the normal. In a clinical trial the computer assessments were found to be less accurate than those of two groups of observers. One reason for these disappointing results is related to the simple criteria used to choose and fit the best "normal" to a particular patient scan. A second reason is the optimization of the scanner/photoscan combination to ^{99}Tc^{m} pertechnetate as a brain scanning agent which results in patient-to-patient variation becoming more important. This reduces the potential of a simple numerical analysis to improve results.

Numerical analysis of radioisotope scans can be divided into two groups:

(1) those which use data manipulation and display systems to present the scan data in a form which is visually more acceptable than the conventional analogue displays:

(2) those which, in addition, incorporate some criteria for abnormality in the analysis and use this facility to interpret the scan.

METHODS OF DATA MANIPULATION

An increasing number of methods of numerical data manipulation and display are available commercially. If the count density is high, image enhancement can be attempted using the techniques described by Iinuma and Nagai (1937) or Brown *et al.* (1971) where iteration or Fourier transform analyses are used to "sharpen" the picture and to overcome the resolution and contrast limitations of the system. For lower count-rates, smoothing algorithms can be used either alone or in conjunction with some image enhancement. Brown (1966) simply replaces the count in each element by the sum of twice the count in the element and the counts in each of the eight surrounding elements. Using a different algorithm, Spraw *et al.* (1966) average the counts according to the collimator response function.

The normal pattern and criteria for abnormality

Other authors have attempted to do more than just construct an image from the original distribution of radioactivity; they have introduced criteria for abnormality to ease the problem of interpretation. Most methods involve comparison of a particular patient scan with one which is presumed to be normal. The "normal" scan is a composite of several scans in which no subsequent clinical abnormality has been demonstrated. Alternatively, where there is sufficient symmetry in the normal anatomy, one side of the patient scan can be directly compared with the other.

The justification for this type of approach lies in its potential ability to demonstrate statistically significant abnormalities which may not be seen with conventional display systems.

This method of "normal" subtraction attempts to imitate the method of analysis used by a radiologist who, when examining a radiograph or a photoscan, compares the picture he sees with his concept of how a "normal" picture should appear. The "normal" must be flexible enough to allow for acceptable biological and statistical variation. Differences beyond these limits will have varying significance which will depend upon their magnitude, position and shape. The analysis described in this paper approximates to this process by choosing the best "normal" from several stored in the computer memory, and by subtracting this from the patient scan. In principle this is the same as comparing a target area with the surrounding background area, but in the case of the "normal" subtraction method the background count is estimated from the separate "normal" scans, rather than by interpolation from surrounding areas.

Previous attempts to consider the normal pattern of uptake

Duggan *et al.* (1964) described a method in which a brain scan is divided into elements, the dimensions of which vary from patient to patient based on external bony structures of the skull. The counts are normalized and compared with a "normal" composed of six scans. Their results showed an improvement in accuracy over black-and-white dot scans, but no significant difference when compared with colour scans.

The method of brain scan analysis described by Popham *et al.* (1970) uses a fixed matrix and several normal scans to allow for variation in head size and orientation. With criteria for abnormality which yield a 5% false positive rate their results show a significant improvement in accuracy over the assessment made by a group of clinical observers.

A similar analysis was described by Dowsett and Perry (1970) and by Dowsett (1972). The present paper discusses further the methods they used and presents the results of the analyses in a small clinical series of scans.

THE TREATMENT OF THE SCAN DATA

The method of data collection and the construction of normal scans have been described previously (Dowsett and Perry, 1970). Scan data are derived from a SELO rectilinear scanner which has a 12.5×5 cm NaI (TI) crystal. Between 6 and 10 mCi of ^{99}Tc^{m} as pertechnetate is used as the scanning agent and is administered intravenously. The basic scan element is 6×6 mm which is half the linear resolution of the collimator used. The "normals" are the arithmetic means of several proven normal patient scans classified in effect by difference in size and shape of the skull outline. Altogether five different "normals" were available for the lateral scans and two each for the antero-posterior and postero-anterior views.

An outline flow chart of the steps taken in the manipulation of this data is given in Fig. 1. The patient scans are read into the computer from paper-tape and the data are smoothed using a simple algorithm covering nine elements. The "normal" scans are also treated in this way.

The patient scan is next normalized to the same average count-density as the "normal" scan and is then "fitted" to the "normal" scan. This fitting procedure is carried out by moving the two scans relative to each other until a minimum value is found for the sum of the modulus of the element-by-element difference between the patient scan and the "normal" scan (the fit "value").

The co-ordinates specifying the position of the fit, together with the fit "value", are stored and the

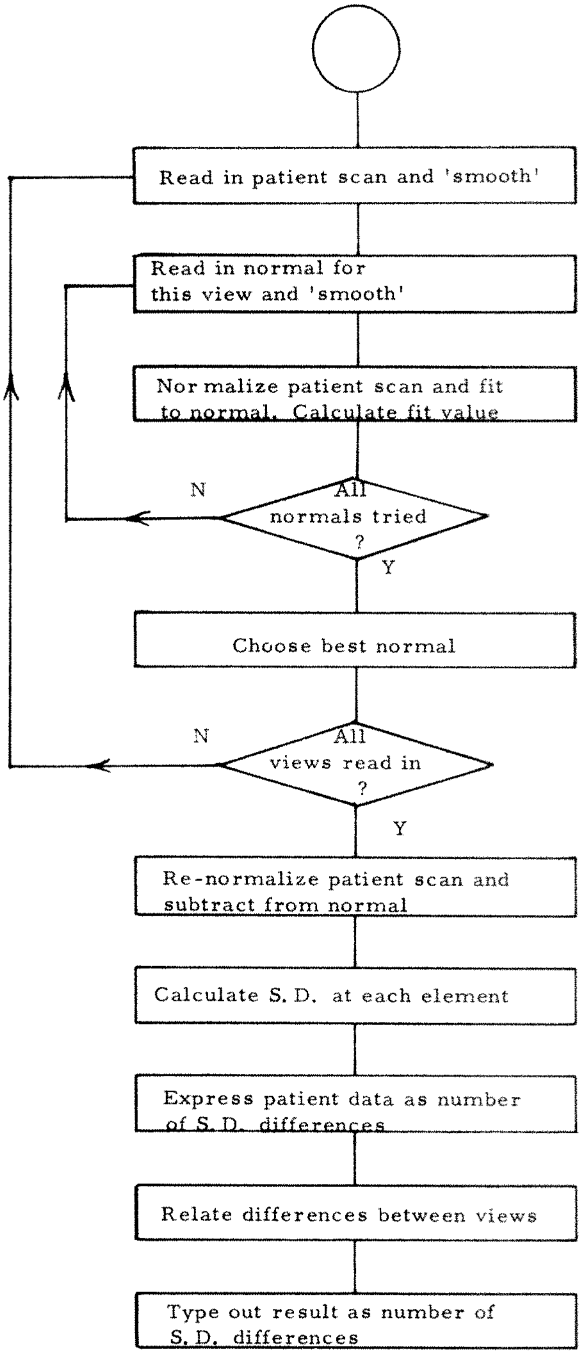
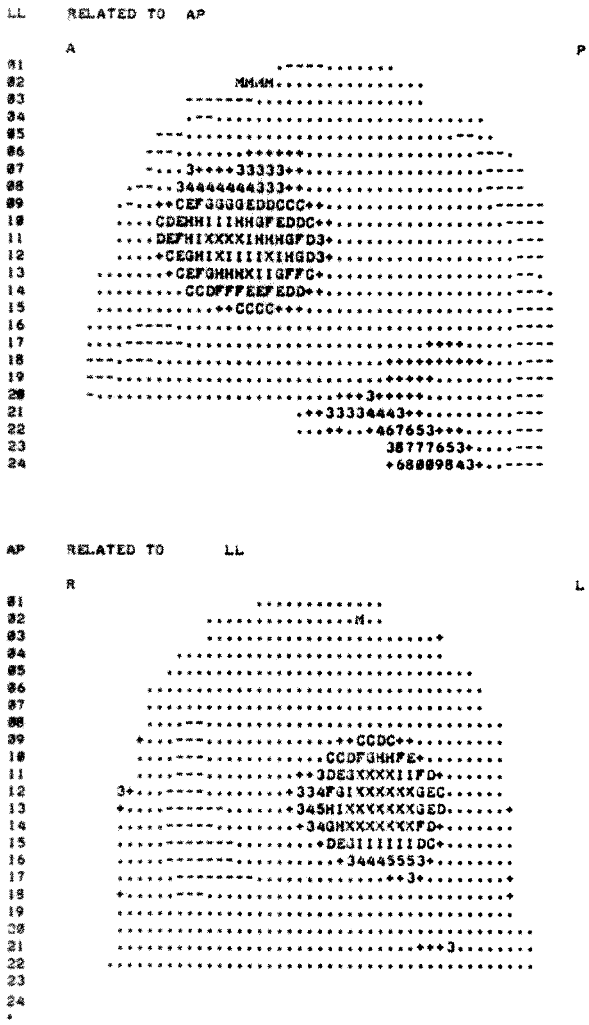

Read in patient scan and 'smooth'
Read in normal for this view and 'smooth'
Normalize patient scan and fit to normal. Calculate fit value
N
All normals tried ?
Y
Choose best normal
N
All views read in ?
Y
Re-normalize patient scan and subtract from normal
Calculate S. D. at each element
Express patient data as number of S. D. differences
Relate differences between views
Type out result as number of S. D. differences

FIG. 1.
Outline flow chart of analysis.

procedure is repeated for the other "normal" scans. The best "normal" scan is defined as the scan which gives the minimum fit "value".

At this stage any further scan views from this patient are read into the computer and processed in the same way. The best "normal" scan for each view is then subtracted element-by-element from the normalized patient scan and the differences are converted to standard deviations. If elements with standard deviations of magnitude three or greater appear in the same line of, say, the posterior half of a right lateral scan, and the right half of a postero-anterior scan, these elements are called "related" and special print-out symbols are used. A typical print-out is shown in Fig. 2.



```
LL      RELATED TO   AP

        A                                                       P
01                             .----.......
02                         MMMM...............
03                    -------.................
04                    .--...........................
05                 ---...........................--..
06                ---.......++++++.................---.
07                -...3++++33333++..................----
08              .--..34444444333++..................----
09             .-..++CEFGGGGEDDCCC++.................-----
10             ....CDEHHIIIHHGFEDDC++.................----
11             ....DEFHIXXXXIHHHGFD3+..................---
12             ....+CEGHIXIIIIXIHGD3+..................---
13           .......+CEFGHHHXIIGFFC+...................--.
14           .........CCDFFFEEFEDD++...................---.
15           ............++CCCC+++.....................----
16          ....----...................................----
17          ....------........................++++.....----
18          ---.---.......................++++++++++....---
19          ---...........................+++++........----
20          -........................+++3++++.........---
21                               .++33334443++.........---
22                               ...++..+467653+++......---
23                                        38777653+....---
24                                        +68889843+..----


AP      RELATED TO       LL

        R                                                       L
01                           .............
02                      ...............M..
03                      ........................+
04                   ............................
05                  ................................
06                ...................................
07                ...................................
08                ....--...............................
09               +...---.............++CCDC++..........
10               ....---............CCDFGHHFE+........
11               ....---.........++3DE3XXXXIIFD+......
12             3+...----.......+334FGIXXXXXXGEC......
13             +....------......+345HIXXXXXXGED......+
14             .....-----.......+34GHXXXXXXFD+.......
15             .....-------........+DEJIIIIIIDC+.......
16             .....-------..........+34445553+........
17             ......--------..............++3+.........+
18             +.....---.............................+
19             ........................................
20             ..........................................
21             ..............................+++3........
22            ...........................................
23
24
.
```

Fig. 2.

Typical print-out of a set of patient scans following analysis. The basic analysis element is 6 × 6 mm giving a maximum matrix of 40×25 elements. To allow the print-out to follow the shape of the skull more exactly the matrix is expanded horizontally 1.5 times. The meanings of the symbols used are:

Symbol	Standard deviations from normal
.	−2 to +1
+	2
3 to 9	3 to 9 unrelated
0	> 9 unrelated
C to I	3 to 9 related
X	> 9 related
—	⩽ −3 unrelated
M	⩽ −3 related

The calculation of standard deviation for each element

The standard deviation of each scan element has two parts:

(a) the sampling error of the counts. This is equal to the square root of the count;

(b) the patient-to-patient variation. This is a proportion of the count which is independent of the count magnitude, but which is dependent on the element size and position.

If C_p is the normalized count from the patient scan for the matrix element under consideration,

C_N is the scan normalized count from the best "normal" scan for the same element (the "normal" scan is the mean of n proven normal patient scans). $\sigma_{C_p}{}^2$ and $\sigma_{C_N}{}^2$ are the contributions to the overall variance due to the finite number of counts recorded, then

$$\sigma_{C_p}=\sqrt{C_p} \text{ and } \sigma_{C_N}=\sqrt{C_N}$$

These relationships are only approximate because C_p and C_N have both been normalized. Nevertheless the normalization factors are always near unity and are certainly much less than an order of magnitude different.

Also, if $\sigma_p{}^2$ is the patient-to-patient variance, then the percentage patient-to-patient standard deviation

$$P=\frac{\sigma_p}{C_p}\times 100$$

Adapting a formula given by Popham *et al.* (1970) the difference, D, between the patient and "normal" scans expressed in terms of the number of standard deviations from the normal is given by:

$$D=(C_p-C_N)\Bigg/\left(\left(\frac{P.C_p}{100}\right)^2+C_p+\left[\left(\frac{P.C_N}{100}\right)^2+C_N\right]\Big/n\right)^{\frac{1}{2}} \quad . \; . \; . \; . \quad (1)$$

The value of P found by Dowsett and Perry (1970) was 10% at the centre of the head rising to 20% at the periphery (over the skull). These estimates were for the single 6 × 6 mm element and were used in the calculations originally reported so as to avoid the necessity of storing values for the variance of the normals, element-by-element.

The smoothing algorithm now used has the effect of increasing the values of C_p and C_N fourfold. P was found empirically to decrease to 6% at the centre of the head and to 12% at the periphery under these conditions.

Using typical values of 400–500 counts per element for C_p and C_N at the centre of the head, and 1200–1500 at the periphery, the denominator of (1) gives standard deviations of 8.0–9.0% and 12.5–13.5% respectively. These vary only slowly for reasonable changes in count-rate and are mainly a function of position.

In order to take into account the variation of σ_p across the scan in a more realistic manner the standard deviation is derived as the sum of two components. One component is constant over the entire scan and the other is made proportional to the gradient at every element in the *normal* scan. The justification for this calculation is that wherever there is an "edge" in the normal scan there is considerable patient-to-patient variation in the position of the "edge". The data at this point must therefore be treated with less confidence. The constants of proportionality for the two components are such that the standard deviation varies from 8% over central white matter to 12.5% at the skull edges. This procedure removes the necessity of storing tables of the value of σ_p for each element of each "normal" scan.

RESULTS OF THE CLINICAL TRIAL AND ITS ASSESSMENT

Analyses of the radioisotope scans of neurosurgical patients were carried out over a five-week period. Altogether 58 consecutive cases were considered. Assessment of the computer print-out was made by one of us (J.G.) some time after the patients had been scanned. Also at this time a "blind" assessment of the photoscans was made (D.U.) and both assessments were *then* compared with the original scan reports and to the subsequnte substantive clinical diagnoses.

TABLE I

THE NUMBER OF ELEMENTS IN ONE BLOCK, IN ONE VIEW, NEEDED TO BE REGARDED AS ABNORMAL TO GIVE DIFFERENT FALSE-POSITIVE RATES

False-positive rate		10%	5%	1%
No. of elements in one view regarded as abnormal	at three standard deviations per element	20	40	200
	at four standard deviations per element	(1)	(1)	2

The criteria for abnormality in the computer scans were derived from an extension of the theoretical considerations given by Haybittle (1966). For an area A of the patient scan which has a value three standard deviations larger than the same area in the normal scan the probability p that this difference is solely due to random variations is equal to 0.0027. If the area of the whole scan is T and it is required that there is a probability p' of having an area A somewhere in the scan greater than three standard deviations, then $T/A.p=p'$. If the area A contains a number of 6×6 mm elements, each of which is three standard deviations from normal, then, assuming patient-to-patient variation is much larger than counting variation, the area A will be three standard deviations from normal. Thus, for a 5% false-positive rate at three standard deviations ($p'=0.05$) $T/A=18.5$, or A is 5.4% of the scan. For a scan with a total of 750 elements a false-positive rate of 5% would be expected if regions of 40 or more elements at three standard deviations difference are considered as abnormal.

Table I shows the number of adjacent elements at either three or four standard deviation difference that are needed for an area to be regarded as abnormal at theoretical false-positive rates of 10, 5 and 1%. Thus, if the criterion for abnormality is taken as either a region of 40 elements at three standard deviations, or one element at four standard deviations, a 5% false-positive rate should be expected. In a few cases positive areas at the periphery of the scans, probably due to a gross mismatch, were disregarded.

The results obtained by the two groups of observers and by computer analysis are compared in Table II. Observer A (D.U.) made the blind retrospective assessment of the photoscan. The data for observer B was derived from the radiologists' reports made at the time of the scan.

DISCUSSION

The results produced by the "normal" subtraction method are less accurate than those of either of the two observers. The false-positive rates are higher than the theoretical level. This, to some extent, is because the results in Table II refer to patients whereas the theoretical calculations are for single pictures and each patient may have up to four scans. Two aspects of this analysis bear further consideration.

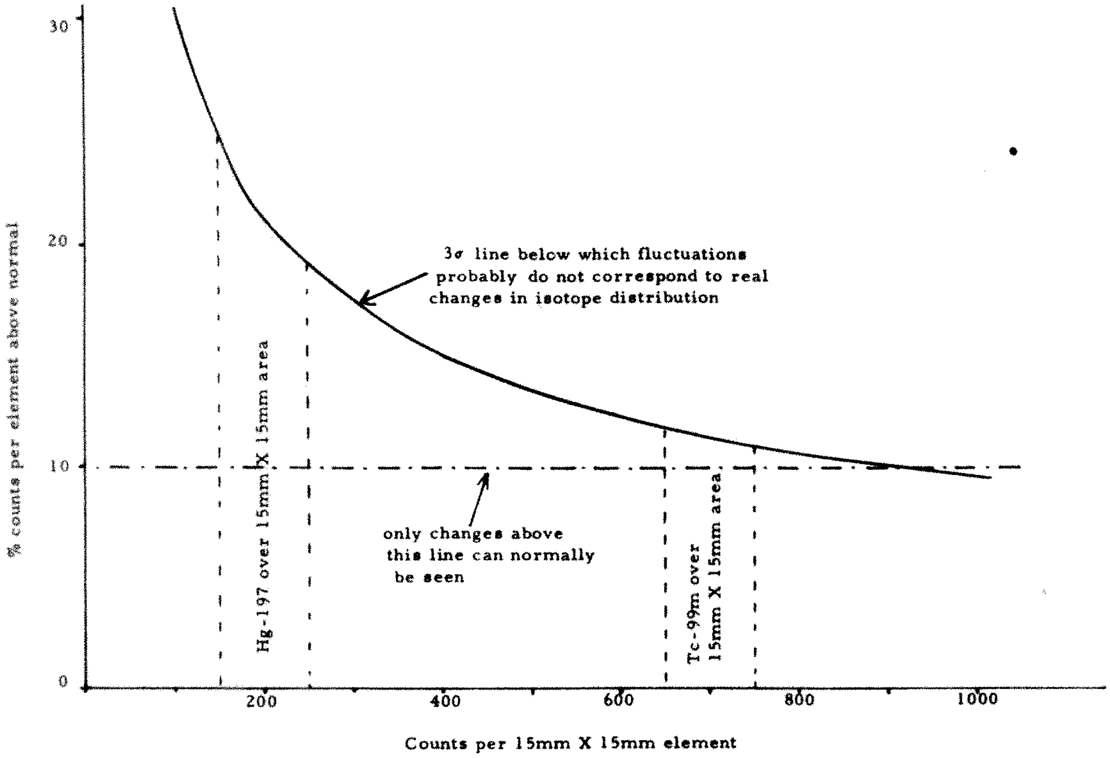


FIG. 3.

The standard deviation (×3) of the counts from a 15×15 mm element plotted as a percentage of those counts and related to the visualization level of a *photoscan*.

TABLE II

SUMMARY OF THE RESULTS OF TWO GROUPS OF OBSERVERS' EVALUATION OF THE PHOTOSCANS AND THE COMPUTER ANALYSES AT THREE THEORETICAL FALSE-POSITIVE RATES RELATIVE TO THE SUBSEQUENT SUBSTANTIVE CLINICAL DIAGNOSIS

	observer *A*	observer *B*	Computer analyses at three false-positive rates		
			10+	5+	1+
True positives	16	19	18	15	14
False positives	0	0	10	7	3
True negatives	26	26	18	21	23
False negatives	16	13	12	15	18

The first relates to the patient-to-patient variance of the normal scan. When this is large the certainty of the analysis is reduced. The performance of the method can be likened to that of an inexperienced observer who, not having an accurate knowledge of the range of normal scans, has to allow a larger margin for error in his assessment, producing an excessive number of false-positive and false-negative reports.

Our method selecting normals takes into account only the size and shape of external bony structures and, in effect, ignores soft tissue areas such as muscle and large blood containing structures. These are clearly seen on most ^{99}Tc^{m} pertechnetate photoscans. In our analysis they merely contribute to an increased patient-to-patient variance rather than helping to differentiate one set of normal scans from another.

The second consideration relates to the visual effectiveness of the scanner display system. If the display is such that statistically significant changes in counts per element are not visually clear, then a numerical analysis of the data may produce better results. The performance of the method described by Duggan *et al.* (1964) which involves relatively low counts per element is impressive when compared with black and white dot scans, but not when compared with colour scans.

Figure 3 shows the percentage increase in counts per 15×15 mm element at the three standard deviation level plotted against the counts per element It has been suggested by Mallard and Wilkes (1968) that increases in count-rate of 10% can just be seen in the normal photoscan. Thus when the number of counts per element is low, as in the ^{197}Hg scans used by Popham *et al.* (1970) statistically insignificant changes can be displayed, so the observer has to judge whether the abnormalities he sees are real or due to counting variation. He therefore has to allow a margin for error and so a proportion of scans may be assessed as equivocal. For the increased counts available from ^{99}Tc^{m} scans, the visualization level and the three standard deviations levels are approximately the same, so any abnormalities seen are likely to be due to the real isotope distribution. Therefore, when using ^{197}Hg, the method of subtracting the normal scan can provide valuable information not clearly defined in the photoscan, whereas with ^{99}Tc^{m} this analysis would seem to be unnecessary.

More generally, if the visualization level of a display is greater than the level of statistical significance then information is lost. If it is smaller than the level of statistical significance the information is presented in a confused form. In both cases the normal subtraction method may improve the results.

CONCLUSION

Compared with the conventional photoscan the results obtained by analysing ^{99}Tc^{m} pertechnetate brain scans using a "normal" subtraction technique have been disappointing. This can be related to the optimization of the photoscan to ^{99}Tc^{m} as the scanning agent where that part of the overall variance arising from counting statistics is reduced, but where that part due to patient-to-patient variation is increased.

The large patient-to-patient variance can only be overcome by increasing the number of normal patterns against which the patient scan can be tested. It follows that the procedures for matching scans would then need to be improved and this would involve feature analysis rather than simple arithmetic comparisons.

The "normal" subtraction method could be useful, however, not as a blanket technique for the analysis of all scans, but as a test of a particular photoscan which appears equivocal to the trained observer. The technique could help the observer to establish the level of significance of the differences seen on the photoscan. The number of occasions where such a further analysis would need to be made are few, and the number of true positives thus brought to light would not justify the cost of the procedure in the routine situation.

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We would wish to thank Mr. George Hales, scanning technician, for his collaboration, and Mr. Ron Howard and Mr. Don Ritchie of the physics department for their redesign and construction of the scanner to tape-punch interface.

We also gratefully acknowledge the continued support given to this project and particularly to one of us (J.G.) by the Cancer Research Campaign.

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$^{99}Tc^m$ — DTPA for the measurement of glomerular filtration rate

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ABSTRACT

Comparison of the blood clearances of ^{51}Cr–EDTA and ^{99}Tc^m–Sn–DTPA, in a series of 45 patients with a wide range of glomerular filtration rates, showed that there was a good correlation between the estimates of G.F.R. obtained using the two chelates simultaneously. The single-injection, single-exponential method of G.F.R. estimation was used, with a correction factor of 0.964 for ^{99}Tc^m–DTPA, which gave a relationship of

$$G.F.R._{Cr} = 2.3 + G.F.R._{Tc} \text{ml/min}$$

with a correlation coefficient of 0.99. ^{99}Tc^m–DTPA is a suitable agent for the estimation of glomerular filtration rate.

Renal scintigraphy and the measurement of glomerular filtration rate (G.F.R.) are both of great value in the evaluation and follow-up of patients with renal disease. ^{99}Tc^m–Diethylenetriaminepenta-acetic acid (Sn) (^{99}Tc^m–DTPA) is an agent widely used for dynamic renal imaging with a gamma camera (Atkins *et al.*, 1973). It has been shown to be handled mainly by glomerular filtration, and preliminary studies in animal and man have suggested that it might be suitable for the measurement of G.F.R. (Klopper *et al.*, 1972).

The estimation of the clearance of ^{51}Cr–EDTA, by the "single-injection, single-exponential" method, as a measure of G.F.R., makes several assumptions but is simple and sufficiently accurate for routine clinical purposes, having an excellent correlation with inulin clearance methods (Garnett *et al.*, 1967; Chantler *et al.*, 1969). This method is now used as the standard in this and many other institutions. The purpose of the present study was to investigate the possible use of the ^{99}Tc^m–DTPA clearance as an alternative to the ^{51}Cr–EDTA clearance in patients having dynamic renal scintigrams.

METHODS AND PATIENTS

^{99}Tc^m–DTPA was prepared from a kit (Diagnostic Isotopes, Inc), using ^{99}Tc^m as pertechnetate (Radiochemical Centre) to give an activity of approximately 100 μCi in 1 ml. ^{51}Cr–EDTA (Radiochemical Centre) was diluted with an aqueous solution of 1% benzyl alcohol containing EDTA in a concentration of 1 mg/ml to give an activity of approximately 100 μCi in 10 ml.

Forty-five consecutive patients attending the Department of Nuclear Medicine as out patients for routine measurement of G.F.R. were studied. All had the purpose of the study explained to them and gave their consent. There was no specific preparation of the patients.

A 21-gauge Butterfly catheter (Abbott) was inserted in a peripheral vein. One ml of ^{99}Tc^m–DTPA was injected via the catheter, followed by 10 ml ^{51}Cr–EDTA. The catheter was flushed through with 10 ml of normal saline and then removed. Preliminary tests showed that this method left no residue of either chelate in the catheter. Ten ml samples of blood were taken from the opposite arm into lithium-heparin tubes at approximately two, three and four hours after injection (the exact time interval was noted).

Standard solutions were made from the same preparations of ^{99}Tc^m–DTPA and ^{51}Cr–EDTA that had been used for injection. Equal volumes of the standards and plasma were counted in a dual-channel automatic scintillation counter, using pulse-height analysis to separate the 140keV peak of ^{99}Tc^m from the 320keV peak of ^{51}Cr. The contribution of the ^{51}Cr in the ^{99}Tc^m window was negligible.

RESULTS

The figure shows the results obtained. It will be seen that the 45 patients had a range of G.F.R.s from 8.4 ml/min to 154 ml/min.

The best-fit straight line, which is shown in the figure, had an equation of

$$GFR_{Tc} = 2.9 + GFR_{Cr} \text{ ml/min} \quad \ldots\ldots\ldots (1)$$

with a correlation coefficient of 0.99, when a correction factor of 0.964 is used for the calculation of GFR_{Tc} in the equation (Chantler and Barratt, 1972)

$$GFR = 0.964 \text{ VD} \div 1.44 \text{ T}_{\frac{1}{2}} \quad \ldots\ldots\ldots (2)$$

(where GFR_{Cr} is the G.F.R. measured with ^{51}Cr–EDTA, GFR_{Tc} is the G.F.R. measured with ^{99}Tc^m–DTPA, $T_{\frac{1}{2}}$ is the half clearance time of the exponential, and VD is the apparent volume of distribution of the tracer).

DISCUSSION

For a compound to be suitable for the measurement of the G.F.R., it is necessary to show that the

G.F.R. measured with that agent is the same as the G.F.R. measured simultaneously using an accepted method. This relation must be true over the full clinical range of G.F.R. Such a correlation has been shown for many other chelates, but not for ^{99}Tc^{m}–DTPA (Molnar *et al.*, 1971).

Correlations have been shown between the G.F.R. measured with ^{99}Tc^{m}–DTPA and inulin clearance in dogs (Klopper *et al.*, 1972), between the ^{99}Tc^{m}–DTPA G.F.R, and endogenous creatinine clearance in man (on different occasions, and with only a fair correlation) (Atkins *et al.*, 1973) and between ^{99}Tc^{m}–DTPA clearance and ^{125}I- Iodothalamate clearance (in 11 subjects with a limited range of G.F.R.s) (Klopper *et al.*, 1972).

Klopper *et al.* (1972) suggested that ^{99}Tc^{m}–DTPA may be significantly bound to blood proteins, and that commercial preparations vary from batch to batch in this respect, which would invalidate G.F.R. measurement. Blaufox *et al.* (1975) state that "the major problems with ^{99}Tc^{m}–DTPA are the complexities of its synthesis and instability *in vitro* and *in vivo*". We have shown that the correlation between ^{99}Tc^{m}–DTPA clearance and ^{51}Cr–EDTA clearance is very close over the full range of G.F.R.s measured simultaneously, using several batches of a commercial kit.

Having shown that a substance is suitable for the measurement of G.F.R., it is conventional for the results to be presented as numerical values which correspond to the inulin clearance. In the case of the single-injection, single-exponential method this requires correction for such factors as the use of venous, rather than arterial, blood and the use of a single, rather than double, exponential analysis. Chantler and Barrett (1972) showed, empirically, that a composite correction factor of 0.87 gave a result numerically equal to the inulin clearance for ^{51}Cr–EDTA. The results above show that a correction factor of 0.964 for ^{99}Tc^{m}–DTPA gives a result numerically equal to the corrected value for ^{51}Cr–EDTA, and thus to inulin.

One difference between ^{99}Tc^{m}–DTPA and ^{51}Cr–EDTA is that the former gives a higher blood activity, particularly when larger doses are used for dynamic imaging. The samples cannot be counted in exactly the same way as when ^{51}Cr–EDTA is used, as the count rate would be too high. This difficulty can be avoided by allowing the samples to decay for 48–72 hours before counting, or by using smaller samples or a less efficient counter.

^{99}Tc^{m}–DTPA has the advantage over other agents for the measurement of G.F.R. that it can be used for imaging. This means that the patient having a dynamic renal scintigram can have a simultaneous estimation of G.F.R. performed with less radiation dosage and no necessity for a separate visit. There is also a reduction in the number of venepunctures needed, which is often an advantage, particularly in children. The work of Fisher and Veall (1975) also raises the possibility that a single blood sample at a known time after dynamic renal imaging with ^{99}Tc^{m}–DTPA may be all that is necessary for estimation of G.F.R.

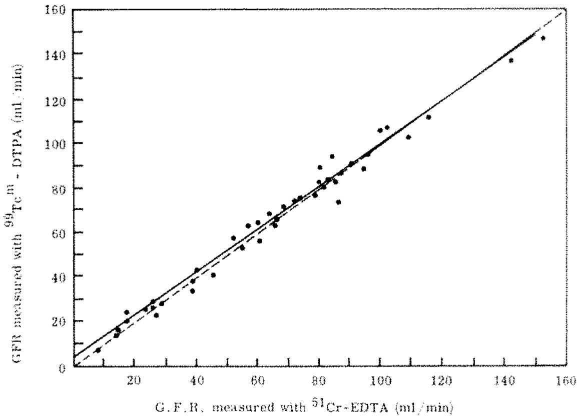

FIG. 1.

Simultaneous measurement of G.F.R. with ^{99}Tc^{m}–DTPA and ^{51}Cr–EDTA. The solid straight line has the equation $G.F.R._{Tc} = G.F.R._{Cr} + 2.9$ ml/min. The dashes indicate the line of identity.

There are several points of interest arising from our findings. If ^{99}Tc^{m}–DTPA is handled only by glomerular filtration, then the renal image obtained using it is a true "functional" image, reflecting the distribution of glomerular filtration. Also, using the approach of Britton (1975), the ratio of ^{99}Tc^{m}–DTPA uptake should reflect the division of renal function between the two kidneys, and we are currently investigating this possibility.

In conclusion, ^{99}Tc^{m}–DTPA is a suitable agent for the routine estimation of G.F.R., as well as being the agent of choice for dynamic renal imaging with the gamma camera, making it the "truly ideal renal function testing radiopharmaceutical" (Blaufox *et al.*, 1975).

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Book reviews

Rational Diagnosis and Treatment. By Henrik R. Wulff, pp. x+182, 1976 (Oxford, London, Edinburgh, Blackwell Scientific Publications), £3·75.

This book is not, as the title may suggest, a practical handbook for the management of patients, written for the benefit of muddleheaded clinicians: it deserves the rather longer title required to represent it as a detailed examination of the sources and measurement of uncertainty in clinical decision making. It succeeds very well in explaining why, and to what extent, "experience is fallacious and judgment difficult". Inevitably, definitions are inexact; classifications change; values have ranges of normality, and abnormality is itself a statistical abstraction; causative factors may be necessary, sufficient or contributory; different reports on the same radiograph may be subject to inter- and intra- observer variation and end as informed opinions; there is no avoiding the inexactitudes. These are difficulties which beset and concern a profession whose lot is to make serious decisions on information of limited accuracy, and which is expected to subject to orderly trial the expectations or misgivings to which they are led by complexes of uncertainty; the uncertainty itself must be given a numerical index. This is what the book is about and, as we might expect, it contains a chapter on the purpose and design of clinical trials and an appendix describing the statistical tests commonly encountered in medical journals.

The clinical reader, who in any case spends most of his professional life trying to give proper weight to a particular manifestation of disease in relation to a particular diagnosis, may question the virtue of dissecting his mental processes in a way that could decompose what is reasonably described as his *art*, or which could deprive him of the confidence required to act, as he often must, in the face of uncertainty. He surely understands that, if a disease commonly presents with one or more of three cardinal features, then some patients may display any one, some any two, and some all three. What need has he, then, of a Venn diagram, to illustrate by three overlapping circles that the various contingencies can be represented by *areas*? The answer is, that he must be prepared to have his acumen processed, to involve himself in information theory and data processing, so that his intracranial software can be got into computer hardware. This book does not pretend to assess the economic consequences or threat of redundancy to be expected from this technological extension of uncertainty: but it will prepare the clinician for the operation without too much pain.

H. B. HEWITT.

Diagnostic Ultrasonics—Principles and use of Instruments. By W. N. McDicken, pp. xii+320, 1976 (London, Crosby Lockwood, Staples), £15·00.

The author's stated objective was to prepare a text which is both comprehensive and technical, yet understandable to non-physicists. There is great need for such a book at the present time, not only because of the rapid growth of diagnostic ultrasound but also because of its inclusion in the radiological and radiographic examinations.

The author states "In ultrasonic scanning the highest quality results are achieved only by the logical and scientific manipulation of the machine controls". This book should certainly enable the novice to achieve this aim.

The author is to be congratulated on his success in achieving his stated aim but the source of his material has resulted in the book having a close resemblance to a series of lecture notes. This does, however, make it very simple for the reader to extract quickly any particular point of information.

This is not a book to be read casually; there is a wealth of information here which should be studied slowly and systematically. Almost every aspect of diagnostic ultrasound is included but the average clinical ultrasonographer will probably find that many of the later chapters can be omitted.

The book is strongly recommended to all those involved with diagnostic ultrasound.

HYLTON B. MEIRE.

1976, *British Journal of Radiology*, *49*, 797–798

Case reports

Diffuse arterial calcification of the uterus. An unusual radiographic appearance

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(*Received December, 1975 and in revised form February, 1976*)

Atheromatous arterial calcification is a frequent radiographic finding, particularly in elderly and diabetic patients (Donner and McAfee, 1960). Only rarely, however, does such calcification involve the uterine arteries (Camil *et al.*, 1967; Fisher and Hamm, 1975).

A patient with unusual pelvic calcification suspicious for psammomatous calcification within a pelvic malignancy, which proved to be diffuse arterial calcification of the uterus, is presented.

CASE REPORT

A 69-year-old white female, presented with 50 pounds of weight loss and increasing abdominal girth over the previous year. Adult onset diabetes had been diagnosed several years earlier and had been easily controlled with diet and chlorpropamide 250 mg daily. Mild cardiac failure and atrial fibrillation were controlled with digoxin 0·25 mg daily.

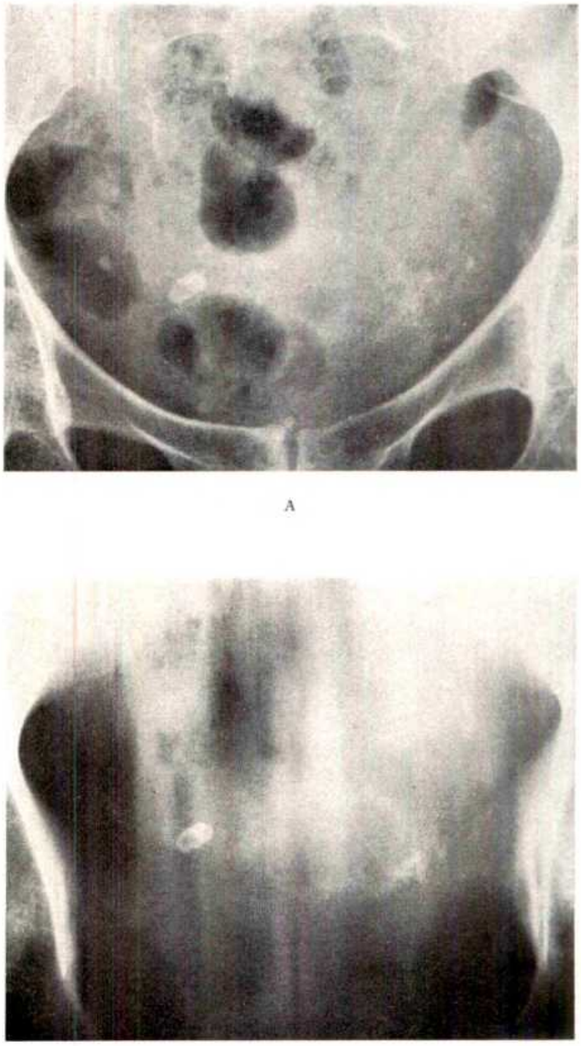
Physical examination revealed a 5 × 7 cm pelvic mass and ascites. Rectal examination showed a hard, non-tender mass involving the rectal shelf. A Papanicolaou smear revealed abnormal cells compatible with adenocarcinoma either of the endometrium or metastatic to it.

Plain abdominal radiography prior to intravenous urography (Fig. 1A) and tomography of the pelvis (Fig. 1B) demonstrated a 4 × 6 cm central pelvic mass with fine punctate calcification. Calcification was present within the iliac arteries and aorta. Intravenous urogram and barium enema were normal apart from displacement of the colon and bladder by the mass.

Dilatation and curettage yielded tissue diagnosed as grade IV anaplastic adenocarcinoma. The origin was difficult to evaluate as there was a suspicion of uterine perforation at the time of curetting. 3,000 R of external pelvic irradiation was delivered over three and one-half weeks and two months later an exploratory laparotomy was performed. Pelvic and peritoneal tumour masses were present and a large mass of tumour involved the greater omentum. A total abdominal hysterectomy and bilateral oophorectomy was performed and the bulk of metastatic tumour masses within the abdomen removed. The tumour was an anaplastic adenocarcinoma most compatible with an ovarian origin. Post-operatively, the patient was started on systemic chemotherapy. No calcification was visible within the tumour masses but the uterus showed diffuse calcification within the small and medium arteries (Fig. 2).

DISCUSSION

Calcification rarely involves the uterine arteries, and when present it usually is in the main trunks



A

B

FIG. 1.

(A) Plain radiograph of the pelvis showing faint calcification within a central pelvic mass. Note calcification within iliac arteries.

(B) Tomogram of the pelvis further defines the calcification but fails to reveal any recognizable form.

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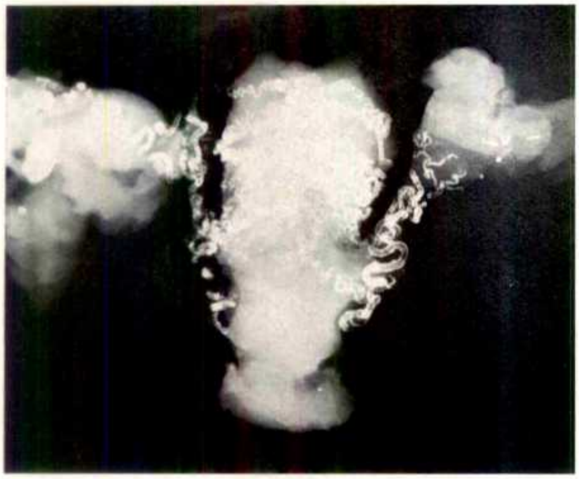

FIG. 2.

Radiograph of the uterus following hysterectomy shows diffuse calcification within small and medium arteries.

in a symmetrical fashion. Most of the reported cases were in diabetics (Camil *et al.*, 1967; Fisher and Hamm, 1975).

In the present case, adult onset diabetes was mild and easily controlled with oral hypoglycemic agents. Athero-sclerotic changes were visible in large abdominal arteries but small vessel and peripheral disease was not a clinical problem. Calcification within the spiral and overlapping small arteries of the uterus made recognition of a tubular character difficult. Because of the size of the vessels involved, the calcification was punctate, stippled and quite faint suggesting a malignancy. Mucinous colonic adenocarcinoma (Shockman, 1973), carcinoma of the bladder (Pang, 1958), papillary serous cystadenocarcinoma of the ovary (Castro and Klein, 1962), leiomyosarcoma of the uterus (Massachusetts General Hospital Case Records, 1962) and malignant mixed uterine tumours (Schabel *et al.*, 1975) have all been reported as showing visible calcification.

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Spontaneous perforation of the extrahepatic bile-duct

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Spontaneous perforation of the biliary tract with bile peritonitis was first reported by Dijkstra in 1932. Since that time over 50 cases have been reported in the indexed literature (Attar and Obeid, 1955; Caufield, 1936; Chen *et al.*, 1973; Colver, 1964; Danelatos-Athanassiadis *et al.*, 1970; Hyde, 1965; Kobayashi *et al.*, 1970; Lilly *et al.*, 1974; Pettersson, 1955; Prévot and Babut, 1970; Snyder *et al.*, 1952).

CASE REPORT

A four-month-old girl presented with scleral icterus, acholic stools, dark urine, and abdominal distension. She was the product of a 39-week pregnancy complicated by two urinary tract infections requiring hospitalization. Pregnancy was terminated by caesarean section because of breech presentation. The infant's birth weight was 2,669 g.

On admission the patient weighed 3,063 g; temperature, 37·1°C (98·8°F); pulse, 116 beats/minute; and respirations, 30/minute. Scleral icterus was present. The abdomen was protuberant with dilated superficial veins visible over the anterior abdominal wall. No abdominal masses were palpable.

Laboratory data included white blood cell (WBC) count of 24,000/cu mm; total bilirubin, 22·8 mg per cent (direct, 14·6 mg per cent); haematocrit, 32 per cent; alkilane phosphatase, 285 mU/ml.; lactic dehydrogenase, 30 mU/ml.; and serum glutamic oxaloacetic transaminase, 95 mU/ml. The urine was positive for urobilinogen but negative for reducing substances. Radiographically, a ^{99}Tc^{m} sulphur colloid liver scan showed normal distribution of radionuclide with the liver slightly displaced toward the midline. B-mode sonography disclosed a large cystic mass occupying the entire right upper abdomen (Figs. 1 and 2). The upper gastrointestinal examination demonstrated displacement of the stomach by a right upper quadrant mass (Figs. 3 and 4) Excretory urography showed partial duplication of the left collecting system.

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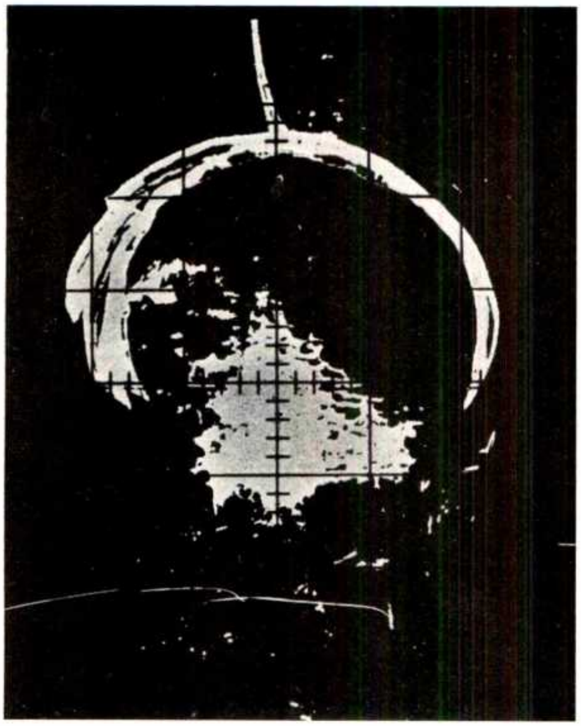

Fig. 1.

Transverse ultrasound scan of upper abdomen performed at intermediate gain setting revealed a large sound transmitting structure extending left of midline. The sonogram is considered to represent composite picture of liver and abdominal mass.

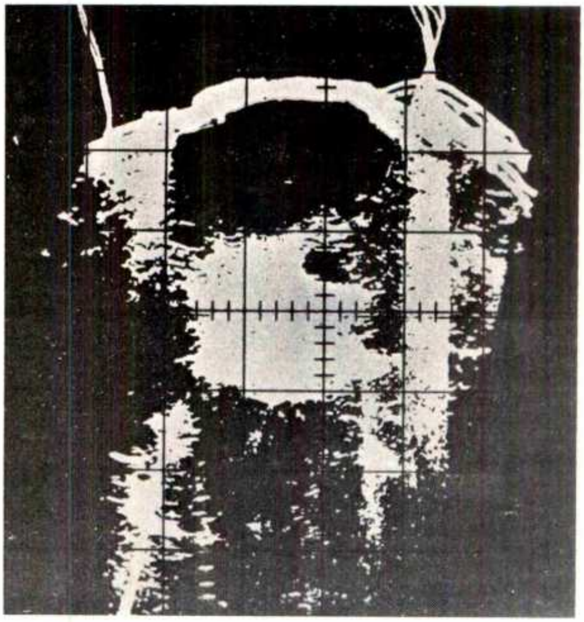

Fig. 2.

Longitudinal ultrasound scan conducted midline location (upper marker=xiphoid; lower marker=umbilicus) and at high-gain setting. A sharp posterior acoustic interface, potentiation of acoustic reflections beyond the lesion, and sonolucency favour cystic mass.

Exploratory coeliotomy, performed on the ninth hospital day, revealed a large bile pseudocyst anterolateral to the liver; this pseudocyst communicated with a smaller bile pseudocyst near the junction of the cystic and common ducts. The cystic duct was totally avulsed from the common duct (Fig. 5). A cholecystectomy was performed and the common duct perforation was closed. A Penrose drain was left in place. Post-operatively, the patient did well and resumed oral intake on the third post-operative day. The drain was advanced on the second day and removed on the fourth day. Total bilirubin on the first post-operative day was 19·8 mg per cent and declined to 3·2 mg per cent by the third post-operative day. The infant was discharged on the seventh post-operative day.

Discussion

Spontaneous perforation of the extrahepatic bile-ducts ranks second only to biliary atresia as a cause of surgical jaundice in the newborn (Lilly *et al.*, 1974).

The aetiology of this condition is unknown; however, a congenital weakness in the wall of the common duct, usually at the junction of the cystic duct and common duct, is postulated (Chen *et al.*, 1973).

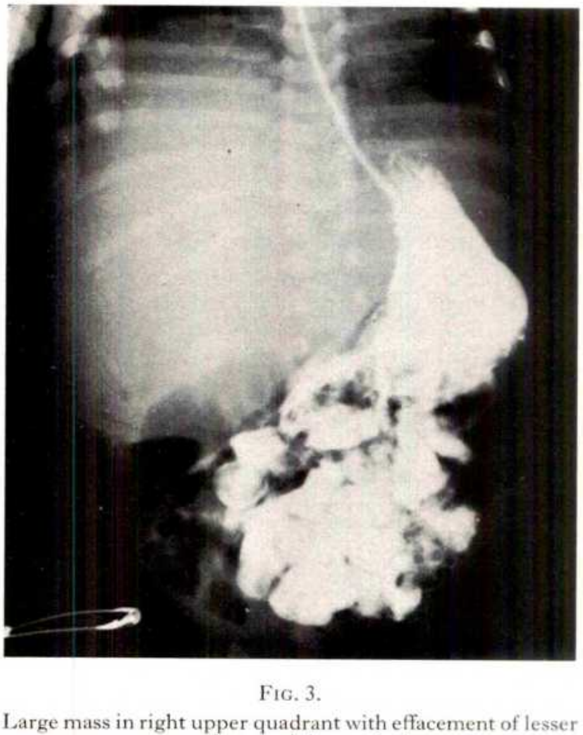

Fig. 3.

Large mass in right upper quadrant with effacement of lesser curvature of stomach by extrinsic mass.

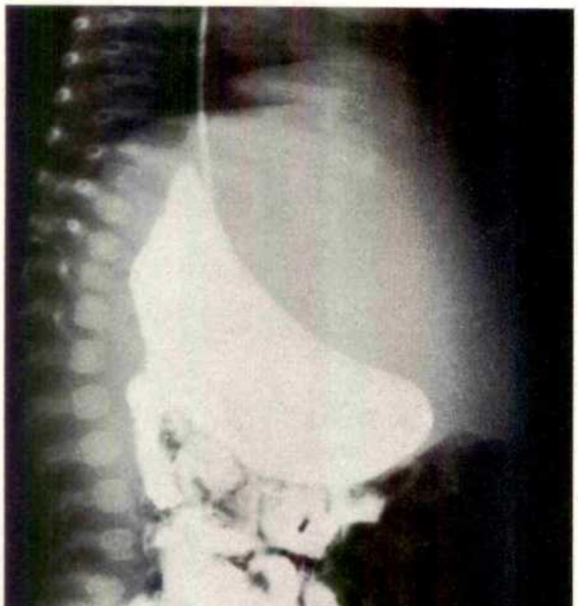

FIG. 4.

Large mass causing posterior displacement of stomach.

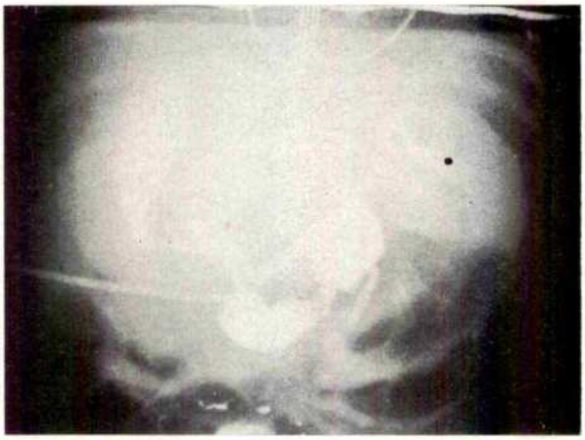

FIG. 5.

Catheter in place in gall-bladder. Contrast medium can be seen in gall-bladder and cystic duct. A bulbous contrast accumulation is seen at the expected junction of cystic and common duct. This accumulation represents the smaller component of encysted bile; the larger bile pseudo-cyst extends into the right upper quadrant. Some contrast medium has entered the duodenum from the common duct as well as intrahepatic biliary radicles in the left liver lobe.

Proponents of this postulate think that this area ruptures or enlarges with increased intraluminal pressure. Our case would represent a rupture, *i.e.*, spontaneous perforation of the extrahepatic bile-ducts. A factor that may be responsible for the perforation of these weakened areas is the presence of inspissated bile and/or stones caused by an excessive pigment load which these infants have the first few days of life. Tiny black flecks of inspissated bile and small stones have been seen at surgery in several cases (Caufield, 1936; Colver, 1974; Pettersson, 1955; Snyder *et al.*, 1952). When the defect does not rupture, but merely enlarges, it may form a choledochal cyst that characteristically presents somewhat later in life and only rarely in the neonatal period (Attar and Obeid, 1955; Danelatos-Athanassiadis *et al.*, 1970).

Patients with perforation typically present after the first few weeks of life with abdominal distension, mild jaundice, acholic stools, and dark urine. Liver function studies are usually normal with the exception of an elevated bilirubin. Upper gastrointestinal series, ^{99}Tc^{m} liver scan, and a ^{131}I Rose Bengal liver function study are diagnostic procedures helpful in identifying the abdominal mass. Sonography is extremely valuable in determining whether the lesion is solid or cystic.

Medical management alone is unsuccessful with a universally fatal outcome (Lilly *et al.*, 1974; Prévot and Babut, 1970). Surgical intervention consisting primarily of exploration with identification of the perforation, followed by simple drainage of the area with a Penrose drain, has been used in the majority of cases (Caufield, 1936; Danelatos-Athanassiadis *et al.*, 1970; Hyde, 1965; Kobayashi *et al.*, 1970). The prognosis is excellent, contingent on early diagnosis and surgical intervention.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Aortoenteric fistula: a late complication of abdominal aortic bypass surgery

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Aortoenteric fistula is a rare late complication of aortic aneurysm bypass surgery. This entity has been discussed in the surgical literature but it has been the subject of only one report in the radiologic literature. The angiographic demonstration of such a fistula has never been reported.

Case report

A 71-year-old man underwent resection of an abdominal aortic aneurysm on August 1, 1973. A straight dacron prosthesis was used which extended from 3 cm below the renal arteries to immediately above the iliac bifurcation. The post-operative course was unremarkable.

The patient was well until one year later when he suffered a myocardial infarction. He recovered from this, and was placed on Coumadin anticoagulation.

On February 12, 1975 the patient experienced abdominal pain and syncope while voiding. A few hours later he passed several grossly bloody stools as a result of which he was admitted to another hospital. An upper GI series demonstrated a scarred duodenal bulb and a questionable ulcer crater. Coumadin was discontinued and an ulcer regimen instituted. The patient remained in the hospital for two weeks during which time there was no further evidence of haemorrhage.

On March 2, 1975 the patient was admitted to our hospital for management of urinary retention which had developed while at the other hospital. Stool guaiac was negative on the day of admission. The next day, however, the patient had two grossly bloody bowel movements, and sufficient blood loss to necessitate blood transfusions. The next several days were marked by intermittent severe haemorrhage presenting as haematochezia. Barium enema and gastroduodenoscopy failed to reveal a source of bleeding. Numerous additional blood transfusions were required.

On March 10, 1975 the bleeding increased and guaiac positive material was vomited for the first time. Aortography at that time (Fig. 1), followed by selective coeliac and superior mesenteric studies, failed to reveal a source of bleeding, despite the fact that large amounts of blood were passed per rectum immediately before and after the procedure. Six hours later bleeding became more severe. The patient developed shock and marked abdominal distention. Repeat aortography was performed (Fig. 2), this time

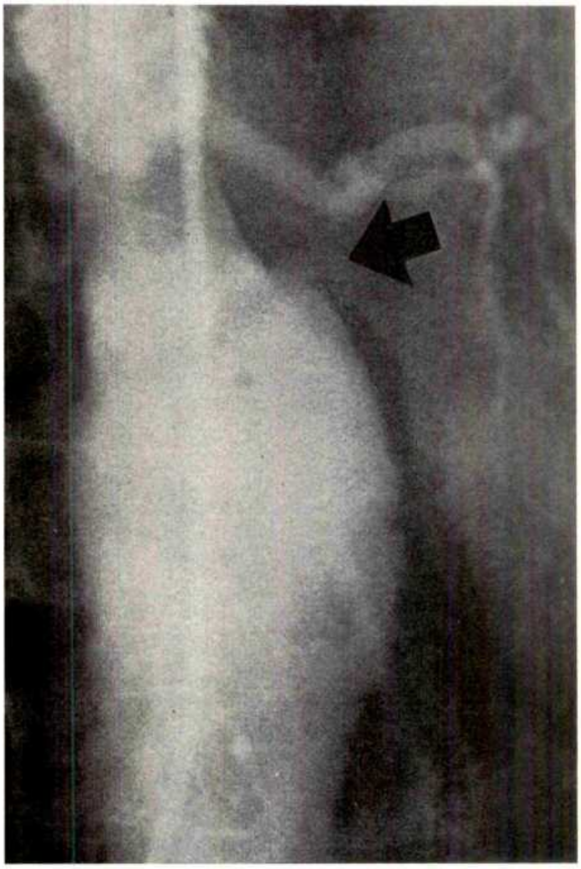

FIG. 1.

First aortogram. Late film showing a small ulcer-like projection of contrast material from the proximal graft suture line (arrow), recognized in retrospect as the site of the fistula.

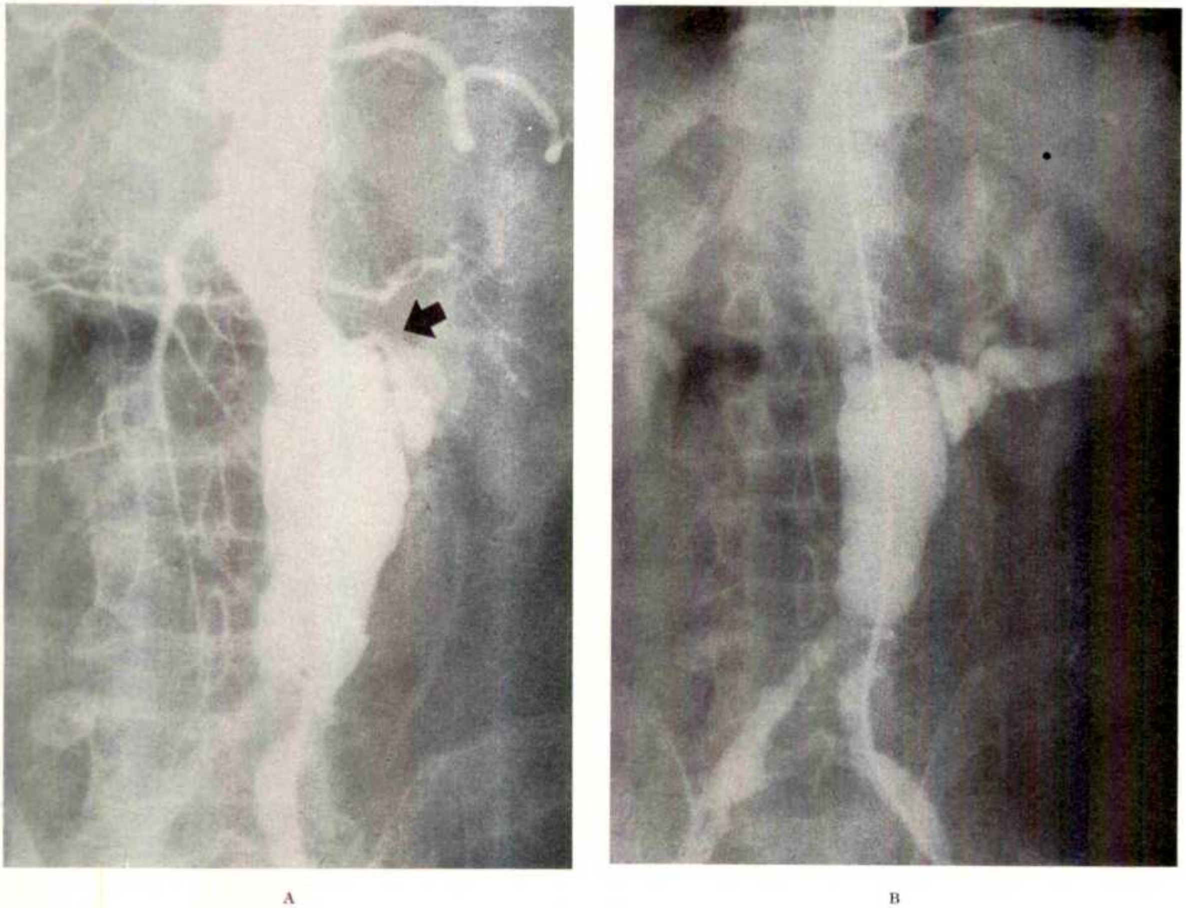

Fig. 2.

Second aortogram. (A) Dye is beginning to extravasate from the fistula (arrow). Note the marked peripheral vaso-constriction in comparison to Fig. 1. (B) Slightly later phase shows a large quantity of dye now extravasated into the jejunum.

demonstrating extravasation of blood from the left side of the proximal prosthetic suture line. A small ulcer-like projection of contrast material from the proximal graft suture line was recognised in retrospect on the first aortogram (Fig. 1).

He was immediately taken to surgery. Upon opening the abdomen no free intraperitoneal or retroperitoneal blood was found. The small intestine was markedly distended with blood. A fistula was present from the proximal suture line of the aortic graft to the mid-jejunum. Repair was attempted but death occurred during the course of surgery.

Discussion

Late complications of bypass surgery for abdominal aortic aneurysm are rare. Nonetheless, when such patients present with gastrointestinal haemorrhage, aorto-enteric fistula should be suspected as this is an infrequent but usually fatal complication (Humphries *et al.*, 1963; Wierman *et al.*, 1966).

Our case demonstrates several features of this complication which have been described in the surgical literature. The initial episode of bleeding occurred 2½ years after surgery. This is not unusual, the interval being greater than one year in the majority of reported cases (Brenner *et al.*, 1974; Humphries *et al.*, 1963; Sheil *et al.*, 1969; Wierman *et al.*, 1966), and 14 years in one case (Elliott *et al.*, 1974). A quiescent period of 19 days followed the first haemorrhage, a pattern described as "classic" by one author (Brenner *et al.*, 1974). Thereafter bleeding was severe but intermittent. While some cases present with a single, continuous life-threatening haemorrhage, about half the reported cases have been characterized by intermittent bleeding (Elliott *et al.*, 1974; Humphries *et al.*, 1963; Sheil *et al.*, 1969). The proximal aortic suture line is the site of involvement in approximately 75 per cent of cases Humphries *et al.*, 1963). Fistulas arising from aortic grafts have all involved the small intestine, although

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in the majority of the cases haemorrhage has been into the duodenum (Elliott *et al.*, 1974; Humphries *et al.*, 1963; Wierman *et al.*, 1966).

Discussion of this complication in the radiologic literature has been limited to a single report of three cases in which barium studies were performed (Ferris *et al.*, 1965). It is unlikely that such studies would regularly demonstrate fistulas of this type. Although potentially more useful, angiography when employed was reported as non-diagnostic (Brenner *et al.*, 1974; Elliott *et al.*, 1974). This was attributed to the intermittency of bleeding. Our first aortogram did not demonstrate the lesion, but review of that study after the second aortogram was performed revealed a small ulcer-like projection of contrast material from the proximal suture line at the site of the fistula (Fig. 1). As this is the most common site of fistulization, particular attention should be paid to this area in future studies, and additional views should be considered when bleeding is not initially demonstrated. As with all angiographic procedures for gastrointestinal bleeding, every effort should be made to study the patient during the actual bleeding episode. In patients with a past history of aortic bypass surgery, aortography should always precede selective arteriograms.

It is hoped that recognition of this clinical entity by radiologists, and awareness that it may simulate more benign forms of gastrointestinal haemorrhage, will result in earlier diagnosis and improved survival.

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Uptake of ^{99}Tc^{m} colloid by intravascular clot

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The uptake of radiopharmaceuticals by blood clot is well documented (Henkin *et al.*, 1974; Morita *et al.*, 1973; Rosenthall and Greyson, 1970; Rosenthall, 1971; Webber *et al.*, 1969; Webber *et al.*, 1973), but in all these instances the radiopharmaceutical was bound either to macro-aggregated albumin (M.A.A.) or to microspheres. We wish to report a case of uptake of ^{99}Tc^{m} sulphur colloid by blood clot.

CASE REPORT

An 18-year-old girl was originally admitted to hospital with abdominal pain in 1973 and a normal appendix removed. She developed acute pancreatitis later that year and was found to be extremely hypercalcaemic. The neck was explored but no parathyroid tumour or hyperplasia discovered. She was transferred to Addenbrook's Hospital on 30.11.73 where she underwent laparotomy and sternal split, in search of aberrant parathyroid tissue, though none was found. The patient remained very ill and required continuous intravenous fluid.

A liver scan using ^{99}Tc^{m} sulphur colloid was performed on 4.1.74 to exclude the possibility of liver metastases. Because of the lack of superficial veins, the radiopharmaceutical was injected through the central venous catheter. This had been inserted through a left arm vein so that its tip lay at the junction of the left innominate vein and superior vena cava. The subsequent scan showed an area of very high uptake behind the sternum (Fig. 1). This was thought to represent a relatively large clot in the superior vena cava, attached to the catheter tip. This was confirmed by a superior vena cavagram performed the following day (Fig. 2) which shows extensive clot in the left innominate vein and superior vena cava, with a leash of collateral vessels present. This catheter was subsequently removed on 7.1.74 without ill effect.

DISCUSSION

The object of recording this case is to report the uptake of sulphur colloid by blood clot. Uptake of M.A.A. and microspheres by venous clot is well documented but we can find only one other reference to the uptake of colloid by probable clot (Helbig, 1973). This was at the site of an indwelling catheter in one of the hepatic veins. In this instance, the appearance of a hot spot in the liver scan was thought to be due either to local uptake by Kupfer cells, or to uptake by clot. In the present case, the uptake of ^{99}Tc^{m} sulphur colloid by blood clot has

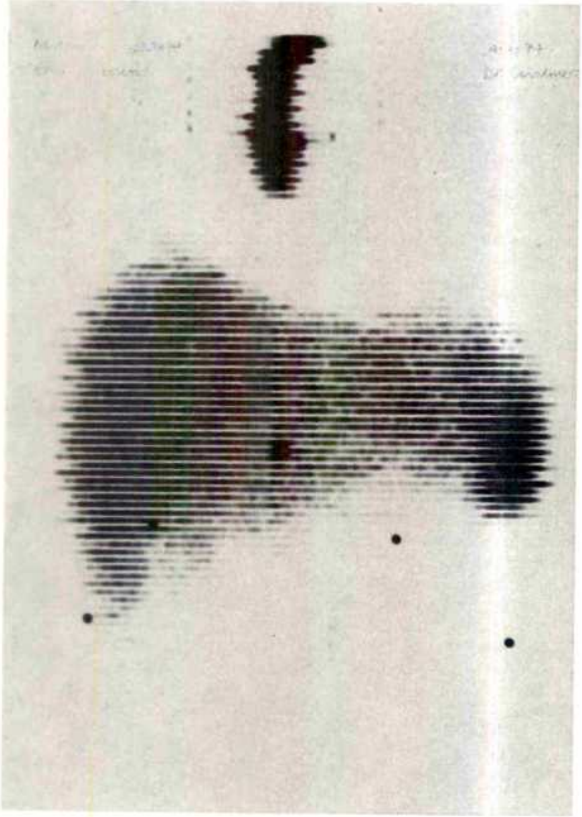

FIG. 1.
Colloid scan showing area of very high uptake behind the sternum.

been confirmed by venography. The possibility of artefacts due to this mechanism should be considered when interpreting scans where the radiopharmaceutical has been injected through an indwelling catheter. This case report also suggests a potential method of investigating venous thrombosis caused by indwelling catheters.

ACKNOWLEDGMENTS

We wish to thank Dr. T. M. Chalmers for permission to publish this case.

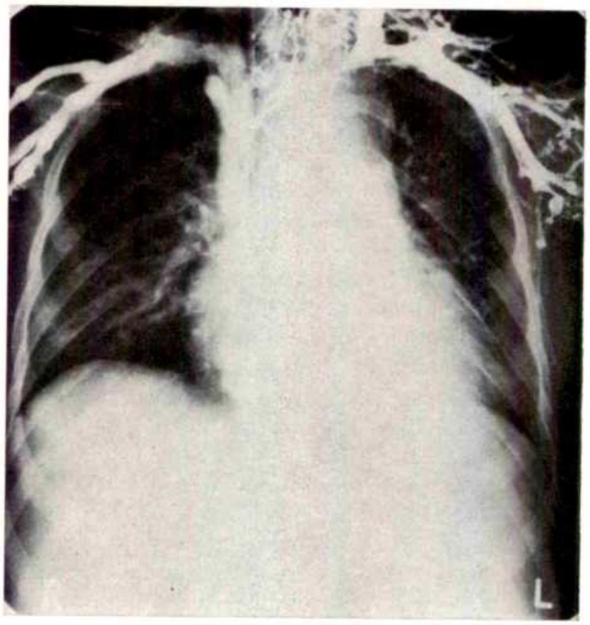

FIG. 2.
Superior vena cavagram showing extensive clot in the left innominate vein with collateral vessels.

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Proceedings of The British Institute of Radiology

The use of hyperthermia and non-ionizing radiations in the treatment of cancer*

Abstracts of papers read at the Radiobiology Work-in-Progress meeting held on Friday, May 21, 1976 in the Reid-Knox Hall, Institute House, 32 Welbeck Street, London W1M 7PG

The interaction of hyperthermia and radiation in CHO cells, by D. D. Loshek, J. S. Orr and E. Solomonidis
Effects of heat shock on the growth of synchronized cultures of *Schizosaccharomyces Pombe*, by J. G. Bullock, W. T. Coakley, and J. L. Moore.
Response of cultured cells to hyperthermia with special reference to thermal tolerance and hypoxia, by E. J. Hall.
Hyperthermia as a modifier of the differential cytotoxic effect of the hypoxic radiosensitizer Ro–07–0582 on mammalian cells *in vitro*, by I. J. Stratford and G. E. Adams.
The effect of hyperthermia and the hypoxic cell sensitizer Ro–07–0582 on the EMT6 mouse mammary tumour, by N. M. Bleehen, D. J. Honess and J. E. Morgan.
The effects of hyperthermia on clostridium oncolysis in experimental tumours, by F. Dietzel and D. Gericke.
Heat sensitivity of rat skin, by Y. Okumura and H. S. Reinhold.
Curability of cancer by heat, by J. A. Dickson.
Coagulation defects following whole body hyperthermia in the treatment of disseminated cancer. A limiting factor in treatment, by R. T. Pettigrew, C. M. Ludgate, R. G. Webber, and A. N. Smith.
Preliminary studies on the effect of whole-body hyperthermia on the immune response of cancer patients and experimental animals, by A. E. Williams, Jean M. Galt, A. P. Gee, R. T. Pettigrew and A. N. Smith.
Experiences with cerebral hemisphere hyperthermia in the treatment of malignant gliomas, by B. H. Cummins, I. McIntosh, R. Greenbaum, R. Cooper, G. Stadden, D. Caddy and A. Winter.
The effects of combined heat and X rays on mouse skin, by Fiona A. Stewart.
The response of developing rat cartilage to combined heat and radiation, by R. Myers and S. B. Field.
Mouse tail radiation necrosis: effect of temperature, oxygenation and dose fractionation, by J. H. Hendry.
Effects of hypoxia and heat on mammary carcinoma in C_3H mice, by Geraldine M. Baker and E. A. Wright.
The effect of ischaemia produced by pressure at different temperatures on the adult mouse tail, by Geraldine M. Baker and E. A. Wright.

THE INTERACTION OF HYPERTHERMIA AND RADIATION IN CHO CELLS

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In an effort to provide a clearer picture of the interaction between hyperthermia and radiation, asynchronous CHO cell survivals for a matrix of doses of radiation and hyperthermia were determined The survival matrix was then analysed by fitting a survival function that was the product of survivals due to hyperthermia alone, to radiation alone and to the interaction of hyperthermia and radiation. This survival function is an expression for the survival surface, a surface in the space defined by the three axes of logarithm of cell survival, hyperthermia dose and radiation dose. The survival surface is a three dimensional extension of the two dimensional survival curve.

For these experiments graded doses of 250kV X rays, ^{60}Co γ-rays or 14.7 MeV neutrons were administered 100 minutes before hyperthermic exposure of graded duration at 42°C. The interaction component was determined to be approximately a first order product term in time and dose. All three types of radiation were sensitized to approximately the same degree.

The X-ray—100 min—hyperthermia experiments were repeated at temperatures of 42°, 43°, 44° and 45°C to examine the temperature sensitivity of the normal hyperthermia and interaction components. The activation energy over this temperature range was 620 kJ/mole for the hyperthermia component, while that for the interaction component was only 360 kJ/mole. This suggests that, for CHO cells, sensitizing events associated with hyperthermia have a different nature from the events leading to hyperthermic sterilization.

EFFECTS OF HEAT SHOCK ON THE GROWTH OF SYNCHRONIZED CULTURES OF *SCHIZOSACCHAROMYCES POMBE*

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The viability of the fission yeast *Schizosaccharomyces pombe* has been examined after exposure to temperatures of 49°C. Half of the population of a logarithmically growing asynchronous population survived heating for 19 minutes. When cells synchronized by a continuous flow centrifugation method of selection were heated for 15 minutes at 20-minute intervals during the two hour cell cycle, the survival varied from 90% during the thermally insensitive stage to 50% during the sensitive stage. The sensitive stage lasts for approximately half the cell cycle and extends from nuclear division to a point early in G_2. The transitions from the sensitive to the resistant stage and back to the sensitive stage occur rapidly. The location and duration of the heat sensitive stage in the cell cycle of *S. pombe* are similar to those reported for the response of this cell to ultraviolet light, and to suicide labelling with ^{32}P.

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RESPONSE OF CULTURED CELLS TO HYPERTHERMIA WITH SPECIAL REFERENCE TO THERMAL TOLERANCE AND HYPOXIA*

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Exposing Chinese hamster cells to prolonged periods at 42.5°C leads to the development of thermal tolerance; the survival curve changes slope at three and a half to four hours and becomes shallower. The kinetics of the elimination of this tolerance have been investigated. In another manifestation of thermal tolerance, prolonged exposure to 42.5°C offers considerable protection from subsequent treatments with acute hyperthermia at 45°C. It has been shown that this is not due to induced cell synchrony.

Hypoxia does not protect cells from the effects of hyperthermia as it does from X rays; indeed hypoxic cells tend to be slightly *more* thermosensitive than aerated cells. The additon of the drug Ro-07-0582, at a concentration of 5 mM, dramatically sensitizes hypoxic cells to hyperthermia while having only a small effect on aerated cells.

HYPERTHERMIA AS A MODIFIER OF THE DIFFERENTIAL CYTOTOXIC EFFECT OF THE HYPOXIC RADIOSENSITIZER Ro-07-0582 ON MAMMALIAN CELLS "IN VITRO"

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There is now evidence that electro-affinic radiosensitizers for hypoxic cells can also function as cytotoxic agents. It is known that there is a large differential between toxicity for hypoxic cells and that for aerated cells. In particular, the 2-nitroimidazole Ro-07-0582 falls into this class of compound and this paper describes the effect of temperature, including the hyperthermia range, on the toxicity of 0582 towards V79-379A mammalian cells *in vitro*.

At 37°C in air this drug does not cause loss of cell viability at concentrations up to 2 mM even when in contact for several days. In contrast, hypoxic cells do not tolerate much lower concentrations of drug even if the contact time is only a few hours. For hypoxic cells, plots of cell survival versus contact time with drug show curves which, after a initial shoulder region, are exponential. When the temperature is raised above 37°C there is a pronounced increase in the slope of the survival curves; for example, at 41°C for 0.5 mM (100 μg/ml) 0582, the slope changes by a factor of 1.9. For cells in air at 41°C, as at 37°C, there is no toxic effect at the concentrations of drug tested.

The results show that hyperthermia increases the differential toxicity of this drug.

THE EFFECT OF HYPERTHERMIA AND THE HYPOXIC CELL SENSITIZER Ro-07-0582 ON THE EMT6 MOUSE MAMMARY TUMOUR

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Work is described in which the 2-nitroimidazole hypoxic cell sensitizer Ro-07-0582 has been shown to be cytotoxic to EMT6 tumour cells when it is combined with hyperthermia. The effect is seen both *in vitro* and *in vivo* and is dependent on drug concentration, duration of exposure to heat and the degree of hyperthermia attained.

In vitro studies, at a constant drug exposure and heating time of one hour using aerobic cultures, show no significant killing at 42°C. Some cell killing after exposure at 43°C is seen but is not potentiated until the drug concentration is increased from 2.5 to 25 mM. At 44°C there is an increased lethality in the presence of the drug at 0.25 mM. When the cultures are rendered hypoxic, by gassing for ten minutes with nitrogen + 5% CO_2, then a marked cytoxicity of the drug (2.5 mM) is seen for one-hour exposures at 43°C.

The cytotoxic effect of hyperthermia on EMT6 tumours *in vivo* implanted into the feet of Balb/C mice was assessed by subsequent preparation of cell suspensions and *in vitro* cloning to determine the surviving fraction. For one-hour exposure in hot water little cell killing was seen up to 44°C water bath temperature. Intraperitoneal injection of 1 mg Ro-07-0582/gm bodyweight of mouse either immediately or 30 minutes before exposure to heat resulted in a considerable increase in cell killing at water bath temperatures of 42-44°C. The effect appears to be greater in large than small tumours and may be related to differences in temperature between the water bath and tumour core.

THE EFFECTS OF HYPERTHERMIA ON CLOSTRIDIUM ONCOLYSIS IN EXPERIMENTAL TUMOURS

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For inactivating tumour cells with sparsely ionizing radiation a sufficient oxygen supply is necessary. A principle of possible tumour therapy, less well-known up to now, however, needs anoxic conditions to be effective; oncolysis by means of anaerobic *Clostridia* (*Clostridium oncolyticum sive butyricum, M55*). The inactivation of hypoxic tumour cells through an ultra high frequency magnetic field and the resulting necrobiotic areas can be used to enhance the germination of intravenously injected *clostridia* spores and thus increase oncolysis in the tumour. We examined the reaction of three different experimental tumours to a four-minute u.h.f. treatment, which increased the temperature in the centre of the tumour up to 43°C. 10^8 spores were given 12 hours after hyperthermia.

Oncolysis of solid Ehrlich-Carcinoma could be increased from 27.6 to 61.3%, of Harding-Passey-Melanoma from 14.7 to 84.1%, and of Methylcholanthren-induced mouse Fibrosarcoma from 1.2% to 22.4%. All differences are extremely significant. Further experiments concerning dose dependence and timing must be made before clinical application can be considered.

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HEAT SENSITIVITY OF RAT SKIN

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Rat skin was selected as a suitable model for the study of local heat toxicity. Application of the air pouch system (Hewitt, 1956), plus immersion of the air pouch in heated water, resulted in a reliable skin temperature with a thermal gradient not exceeding 0.5°C. Temperatures between 42 and 47°C and exposure times ranging from ten minutes to three hours were employed. The animals were examined twice weekly for three weeks for signs of damage. From the various grades of damage, it could be derived that the temperature/time relationship followed the expression $t = a. b^T$ with a b value of 0.51• (t = exposure time, T = temperature in °C). This made possible the reduction of the range of times and temperatures to the equivalent temperatures for a one-hour exposure. The results were calculated by assigning numerical scores according to the RIDIT system (Bross, 1958). It seems that the degree of damage increases stepwise with increasing heat dose.

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These results can also be tabulated by grouping the degrees of damage and deriving the average temperature at which such damage occurs. This is shown in Table I. It can be seen from this table that damage increases sharply with temperature and that, for rat skin, temperatures over 44°C result in permanent damage.

TABLE I

Symptoms	Temperature	Time
a. Normal skin	42.5	60 min
b. Delay of hair growth or or thinning of hair	43.6	,,
c. Slight epilation	43.9	,,
d. Moderate epilation and/or slight induration	44.1	,,
e. Severe epilation and/or moderate induration	44.3	,,
f. Heavy induration and/or breakdown of skin	44.8	,,

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CURABILITY OF CANCER BY HEAT

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Many types of animal cancer cell have been shown to be selectively damaged *in vitro* by heat (42°C) (Cavaliere *et al.*, 1967). *In vitro* sensitivity correlates with tumour response in the host if the heating is adequate in terms of temperature and duration of application, and the host can be cured of cancer even after the tumour has metastasized (Dickson and Muckle, 1972). Although heat damage becomes more pronounced with temperatures in excess of 42°C, the differential effect on cancer cells is lost, and host tolerance becomes a problem due to deleterious effects on normal tissues. The metabolism of approximately 30% of human tumours examined as slices was inhibited at 42°C, and there is evidence that heat can cause tumour destruction in the patient (Dickson and Suzanger, 1976). Potential curability of human cancer by heat alone remains an open question, however, since it depends upon the use of a degree of heating adequate for the stage of the disease (host tumour burden), and the often assumed but unproven vulnerability of metastases to 42°C. With human cancers treated by hyperthermia to date by regional perfusion (Cavaliere *et al.*, 1967; Hall *et al.*, 1974) or by total body heating (Pettigrew *et al.*, 1974) recurrence has been a feature of all reported series. The only method known to have cured disseminated malignant tumours by hyperthermia was injection of Coley's Toxins. Pyrexia was merely one component of this therapy, stimulation of the host immune response and a direct deleterious action of the bacterial products on the cancer cells probably being involved. Curability of cancer in humans by heat, alone or as adjuvant therapy, will depend upon greater knowledge of the part played by host response factors and methods of influencing them favourably, as well as the development of better heating techniques.

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COAGULATION DEFECTS FOLLOWING WHOLE BODY HYPERTHERMIA IN THE TREATMENT OF DISSEMINATED CANCER. A LIMITING FACTOR IN TREATMENT

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Experimental studies have shown that some tumour cells may be more sensitive to heat than normal cells. The hyperdynamic circulation which occurs during whole-body hyperthermia causes a rapid absorption of breakdown products which may result in a consumptive coagulopathy. The coagulation status was studied in 43 patients undergoing whole body hyperthermia for disseminated diseases. No decrease was found in most clotting factors, but there was a marked fall in platelets following initial treatment fractions over 300 deg. minutes in patients with sensitive tumours. The degree minute was defined as the number of minutes that the body core temperature was at 41°C and is a factor representing the area under the temperature – time curve above 40°C. Subdivision of treatment into increasing fractions was required to prevent excessive disseminated intravascular coagulation. Patients with non responsive tumours had a fall in platelet count after the first treatment but not after subsequent treatments. Patients with responsive tumours showed a fall in platelet count after each increasing fraction, averaging 50% of the pretreatment value.

PRELIMINARY STUDIES ON THE EFFECT OF WHOLE-BODY HYPERTHERMIA ON THE IMMUNE RESPONSE OF CANCER PATIENTS AND EXPERIMENTAL ANIMALS

By A. E. Williams, Jean H. Galt, A. P. Gee, R. T. Pettigrew and A. N. Smith

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The effect of whole-body hyperthermia (41–42 deg.) on the general immunocompetence of patients with advanced malignancy and of normal rats is being studied. In both humans and rats, hyperthermia causes a lymphocytopenia followed by a granulocytosis with a return to control values within four days. However, patients with tumours responding to hyperthermia show an increase in absolute numbers of circulating T cells. The lymphocyte response to PHA is depressed after hyperthermia in both rats and humans. At three days, the response of human lymphocytes is above pretreatment levels, but is still partially depressed in rat lymphocytes. In anaesthetized control rats, a less severe and shorter lasting lymphocytopenia is produced. PHA responsiveness is not depressed. During the granulocytosis in patients there is an increase in the number of actively phagocytosing cells. Antibody-dependent cytotoxicity of both lymphocytes and granulocytes is severely depressed by heating *in vivo* or *in vitro*.

The results of this pilot study suggest that the possible effects of hyperthermia on the immune response should be considered when assessing the clinical application of this mode of therapy.

EXPERIENCES WITH CEREBRAL HEMISPHERE HYPERTHERMIA IN THE TREATMENT OF MALIGNANT GLIOMAS

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Malignant gliomas are rapidly lethal despite surgery, radiotherapy and chemotherapy. If they can be debulked, the survival time is enhanced. Usually peripheral spread of tumour invades vital areas of brain, precluding surgical excision. Gliomas very rarely metastasize.

We have devised a technique of local perfusion of cerebral hemisphere containing the tumour, raising the temperature to 42°C over two hours. This has been used in five patients with inoperable malignant gliomas.

At the first stage, after biopsy confirmation of the malignancy of the tumour, a craniotomy is performed, the bone flap being removed and saved for replacement later. Two thermistors are placed in the tumour and one on the brain. A subdural pressure transducer and ventricular catheter are inserted. The patient is then monitored for three days.

At the second stage, under general anaesthesia, the carotid artery is cannulated, clamping off the external branch. A Xe^{133} blood flow study (CBF) is made as a control. The cannulae are linked to a cardiac pump and heat exchanger after anticoagulation of the patient. The minute volume of the bypass circuit is brought up in 50 ml/minute steps until the control CBF level is reached. The carotid blood is then slowly heated until a tumour temperature of 42°C is reached. The heat exchanger temperature rarely exceeds 43°C and haemolysis is minimal.

Continuous monitoring of the intratumour and brain temperature, intracranial pressure and blood pressure are logged on chart and tape. Continuous bilateral EEG records are taken throughout.

The tumour temperature is maintained at 42°C for two hours. The ipsilateral EEG usually becomes very abnormal during this stage but rapidly recovers on cooling.

Two patients died with 48 hours. One survived five months, another twelve months. One patient survives five months later, having achieved very considerable tumour lysis.

Hyperthermia may prove a useful adjunct to present therapy of malignant gliomas.

THE EFFECTS OF COMBINED HEAT AND X RAYS ON MOUSE SKIN

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The combined effects of heat and X-irradiation on normal mouse skin were investigated. The left hind legs of mice (five mice per dose point) were heated in a water-bath at temperatures between 37°C and 43°C for an hour. Irradiations were performed in the middle of this heating period.

X-ray dose reduction factors for a given level of skin reaction were obtained for the various temperatures. These factors are called thermal enhancement ratios. The maximum TER obtained was 2.0 at a temperature of 43°C for one hour.

The relative effectiveness of heating before and after X-irradiation was also studied. One hour heat (42°C) was given at various times (0 to 24 hours) before and after X-irradiation. When heat was given up to six hours before irradiation there was still some enhancement of the radiation damage (TER). When heat was given after X-irradaition there was a much more rapid loss of sensitization. For an interval of three hours or greater between X rays and heat there was no thermal enhancement.

We concluded that heat does sensitize skin to X rays. If the two modalities are not applied simultaneously the thermal enhancement will depend on the sequence of heat relative to X rays and the time interval between the two applications. The potentiating effect of heating is lost more rapidly when it follows irradiation than when heat precedes irradiation.

THE RESPONSE OF DEVELOPING RAT CARTILAGE TO COMBINED HEAT AND RADIATION

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Much work on the combined effects of heat and radiation has been carried out on cells *in vitro*. In order to carry out an *in vivo* study of normal tissue, the growing tail-cartilage system of Wright and Howard-Flanders (1966) and Dixon (1967) was investigated. Stunting of growth of the vertebrae in the tails of seven-day rats caused by wet heat and X rays was measured. Thermal enhancement ratios (TERs) were obtained where

TER = Dose of X rays required to produce a given level of stunting
÷ Dose of X rays with heat treatment, required to produce the same level of stunting

No thermal enhancement was obtained after one hour's heating at 38°C or 41°C. 42°C for one hour produced a TER of approximately 1.5, and 43°C for one hour a TER of approximately 1.7. Similar TER's have been obtained for other normal tissue systems (mouse intestine and skin).

The combined effect of 43°C for one hour plus 1000 rad of X rays was found to be synergistic if the heat was applied first, but not so if the X rays were given first. When X rays were applied subsequent to heat, potentiation of X ray damage was still significant at eight hours. When heat was applied four hours or more after X rays, the combined effect was little more than that of X rays alone. The implication of these results is that the repair of sublethal damage after a first dose and subsequent accumulation of sublethal damage for a second dose is less for heat followed by X rays than for X rays followed by heat. However, the precise relationships may depend on the relative doses of X rays and heat.

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MOUSE TAIL RADIATION NECROSIS: EFFECT OF TEMPERATURE, OXYGENATION AND DOSE FRACTIONATION

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The healing or the presence of permanent tissue breakdown by six weeks after X-irradiation of a 2 cm mid-tail region of the mouse has been used as an experimental model for necrosis. The dose required for tail healing or necrosis in half of a group of mice (the ND_{50}) has been estimated for various conditions of irradiation and several fractionation schedules.

When the irradiation jig is pre-heated to known levels, and the tails are positioned in the jig five minutes prior to irradiation, the ND_{50} is reduced by about 100 rad for every degree C. rise above ambient, over the range 21–41°C. The change from ambient to 37°C is due largely to the oxygen status of the target tissues, as the ND_{50} ratio (clamped tail/tail in air) rises from 1.5 at ambient to 2.3 at 37°C.

Split-dose experiments (24 hour interval) show a recovered dose (D_2–D_1) of about 700 rad in air at ambient, and this effect is greater at 37°C. For this system (D_2–D_1) or D_2/D_1 is not a good predictor of the effects of further dose fractionation, as the ND_{50} ratio (ambient/37°C) at 2 fractions/2 days differs from the similar ratios at 1F/1d, 5F/5d, 10F/12d, and 15F/19d.

EFFECTS OF HYPOXIA AND HEAT ON MAMMARY CARCINOMA IN C_3H MICE

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First generation transplants of C_3H mouse mammary tumour have been treated at temperatures between 41.0° to 42.5°C in combination with pressures sufficient to cause various degrees of ischaemia.

Treatment for 90 minutes at pressures of 80 mm Hg or more, which completely exclude blood from the hind limb bearing the tumour, has resulted in the cure (lack of recurrence for 150 days) of between 43% and 70%. With these pressures damage to the foot is common, although not inevitable. The use of lower pressures reduces foot damage but the number of cures achieved is less.

A treatment schedule involving intermittent pressure application has been found to be advantageous in that foot damage was virtually eliminated. The pressure was reduced or removed for three five-minute intervals during the course of the 90 minutes of treatment. Blood was thus allowed to flow to the foot during the periods of low pressure. A cure rate of 27% has been obtained with this method.

The size of the cuff used for this treatment was limited by the length and shape of the mouse's hind limb. It was not, therefore, possible to be sure that the whole of a tumour in this position was maintained at the desired temperature. Since this could have accounted for some or all of the recurrences, we have now tranplanted tumours onto the tails of the mice so that a longer cuff can be used and uniform heating assured. So far 20 tail tumours have been treated by this procedure. None of the tails has shown any damage and the first five animals have had no recurrence of tumour for 100 days.

THE EFFECT OF ISCHAEMIA PRODUCED BY PRESSURE AT DIFFERENT TEMPERATURES ON THE ADULT MOUSE TAIL

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The tails of adult C_3H female mice were compressed for various lengths of time in a rubber lined capsule at 250 mm Hg pressure, using water which was circulated through the capsule at various temperatures from 30°C to 50°C.

Necrosis and detachment of the distal parts of the tails was noted and graphs constructed in which (a) the longest time at any temperature which was followed by survival of the tail, and (b) the shortest time at any temperature which resulted in loss of the tail, were plotted against temperature. An Arrhenius plot suggested that at least two major factors were operating to cause tail necrosis. The results may be useful in deciding on the maximum time that normal tissue can be compressed at any temperature without severe damage.

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Short communication

Radiation exposure from EMI scanner—multiple scans

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(*Received January, 1976*)

The measurement of radiation exposure to the skull for a single complete scan has been reported by Perry and Bridges (1973). They conclude that the exposure to the cranium for a complete series of transverse axial scans is between 1.0 and 2.5 R. This result follows from the assumption that there is a negligible contribution to the dose due to scattered radiation from adjacent scans. Indeed, the narrow, highly collimated beam of X rays should exhibit narrow beam characteristics with a backscatter factor approaching unity. However, as the beam scans back and forth moving in an arc around the head, and as additional scans are performed at different levels, the area irradiated by the X-ray beam becomes considerably larger. The size of the collimated beam is about 2.5 cm × 0.3 cm, but the actual size of the field over a single traverse of the X-ray beam is 2.5 cm × 25.6 cm. The routine skull examination includes three or four complete scans performed at 2.5 cm intervals. Thus the total field size for a full series of scans is such that there is considerable backscatter.

A series of experiments was performed to determine the effect on the dose of multiple adjacent scans. Measurements were made using encapsulated LiF powder which was calibrated against an ionization chamber at 120 kV, 3.4 mm Al HVT. Capsules of LiF powder were distributed around the circumference of a Rando phantom skull in the plane of the scan. Two series of measurements were made, both under normal operating conditions of 120 kV, 32 mA, namely (1) single scan (section No. 2 of Rando phantom), and (2) three adjacent scans—one scan as in (1) and one scan in each adjacent plane (2.5 cm inferior and superior to section No. 2). Measurements were performed in section No. 2 for each series.

Results are shown in Figs. 1 and 2. Subsequent measurements on patients have verified these phantom data. No measurements were made inside the skull and exponential attenuation is assumed in order to obtain the isodose lines.

Results for the single complete scan agree very well with those of Perry and Bridges (1973). Results for the multiple scan indicate that scatter doses from adjacent scans are not negligible. The actual exposure to the cranium for a series of three transverse axial scans is 40 to 100% higher than that reported for a single scan, reaching a peak value of 4.5 R for the size of skull under consideration. This peak value represents an increase of about 50% over that obtained for a single scan. Measurements indicate that the addition of a

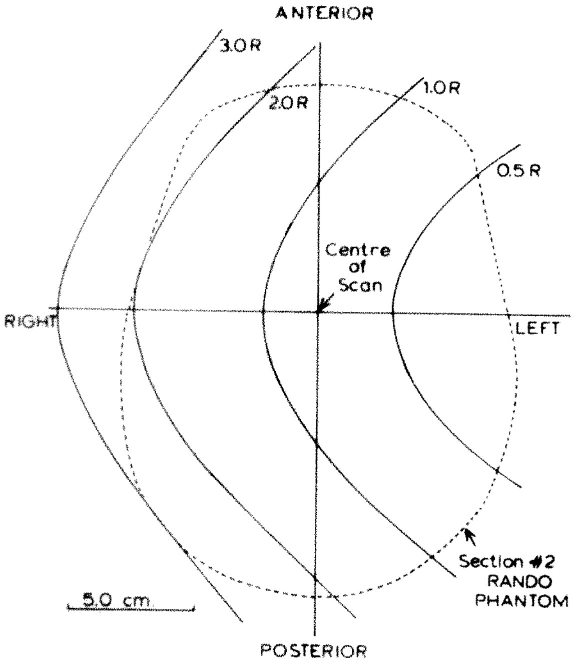

FIG. 1.

Iso-exposure curves in Section No. 2 Rando phantom for a single complete scan, 120 kV, 32 mA.

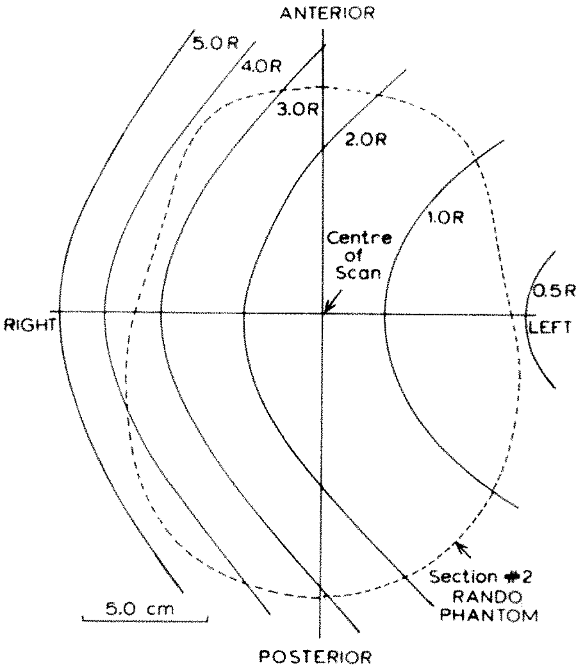

FIG. 2.

Iso-exposure curves in Section No. 2 Rando phantom for three adjacent scans, 120 kV, 32 mA. Exposures shown are in the central scan section.

fourth scan to a skull series increases the peak exposure by a further 10%, thus reaching a value of about 5.0 R. If an additional series of scans is required with contrast media the exposure to the skull will be doubled, becoming about 10 R.

Computerized transverse axial scanners capable of scanning different body sections have been introduced by several manufacturers. Although the general principles of image formation are the same, the techniques used to obtain the data vary. The scanning of thicker body sections may involve higher patient exposures. As a result of our investigations on the EMI scanner, we suggest that patient exposures resulting from transverse axial body scanners be thoroughly evaluated, particularly with regard to sensitive body structures.

In summary, the dose to the cranium of patients undergoing routine skull examinations on the EMI scanner is higher than previously reported. Although doses measured for a single scan are consistent with published data, it has been shown that contributions due to scattered radiation from adjacent scans are significant. Exposure to the cranium for a series of three transverse axial scans will reach a peak value of 4.0 to 5.0 R depending upon the size of the skull. An additional series of scans with contrast media will increase this exposure to about 10 R. Different models of computerized brain or body scanners will require independent evaluation with regard to patient exposure since the techniques of scanning vary.

We would like to thank Dr. M. Banna, Neuroradiologist, McMaster University Medical Centre, and Mr. C. Porteous, Electronic Engineer, Hamilton General Hospital, for their co-operation and assistance in obtaining the measurements.

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Book review

Radiation Research, Biomedical, Chemical and Physical Perspectives. Edited by Oddvar F. Nygaard, Howard I. Adler and Warren K. Sinclair, pp. 1381, 1975 (Academic Press Inc., New York, San Francisco, London), £20·55.

This volume is a record of the proceedings of the Fifth International Congress of Radiation Research held at Seattle, USA in July 1974. The sponsor for these meetings is the International Association for Radiation Research which holds such meetings every four years, the last two having been held at Cortina, Italy (1966) and in Evian, France (1970).

The proceedings open with special addresses given by Dr. Dixy L. Ray, Chairman of the US Atomic Energy Commission and Dr. J. W. Boag who gave the twelfth Failla Memorial Lecture on the subject of the "Timescale in Radiobiology". This provides a useful introduction to the methods used to investigate the radiobiological timescale, in particular pulse radiolysis and fast mixing studies carried out by Adams, Michael and their colleagues at the Gray Laboratories to investigate the effects of oxygen and other radiation sensitizers which are reported more fully in a symposium. There follow reports of five plenary sessions which cover a wide range of topics. Energy needs, prospects for fusion power and technological applications of radiation are discussed. Also there are sessions covering aspects of human radiobiology and possible hazards of exposure to radiation in the context of other environmental pollutants which is also dealt with at greater length in symposia.

The symposia which form the main part of this bulky volume cover an even wider range of topics, from basic physics of the interaction of radiation with matter to effects of radiation on whole animals including man. Of particular interest to the radiotherapist may be the symposium on the use of heavy particles in radiotherapy, in which some experiences in the use of neutrons for therapy in the USA are described. One symposium given by Rogers deals with results from the Middle Atlantic neutron therapy trial using the Naval Research Laboratory cyclotron and another given by Hussey, Fletcher and Caderas reports preliminary findings with the Texas A and M variable energy cyclotron. Other symposia describe the effects of heavy particles in relation to the oxygen effect and other radiobiological phenomena.

Also on the subject of high LET radiation there is a section dealing with the possible effects of cosmic radiation bombardment of man during space flight including results of "Biostack" experiments flown on board Apollo 16 and 17 missions.

In keeping with the proceedings of previous meetings there are major contributions in the field of radiobiology. Effects of radiation at the genetic, cellular and animal level are described including carcinogenesis, hypoxic cell sensitizers, cell kinetics after irradiation, and repair processes. Although much of the material is also published elsewhere it is useful to have a collection of such papers which summarize to date the findings of leading scientists within each field. For example, Okada reviews current work on cellular repair processes being carried out in Japan.

Although this volume of Radiation Research does not include the proffered papers at the meeting and only encompasses the plenary sessions and symposia it must be difficult, if not impossible, for anyone to grasp the entire scope of the work described. There is considerable overlap between the sections of symposia and the divisions into these sections seem somewhat arbitrary. However, each field of radiation research appears to be fairly well represented so the reader is left with a balanced view of the subject.

The proceedings are rounded off with excellent reviews in each major area: physics, chemistry, cellular and subcellular radiobiology, and tissue and animal biology, which effectively highlight main areas of current research within each field and help the reader to put the vast amount of information presented into some perspective.

P. E. BRYANT.

1976, *British Journal of Radiology*, *49*, 812

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

Amniography in the Early Diagnosis of Hydatidiform Mole

I read with some interest Drs. Ang, Chan, and Ng's paper on the diagnosis of hydatidiform mole in a recent issue (*British Journal of Radiology*, *48*, 979, 1975). I suggest that the conclusion of the paper might have been that amniography should be performed to document this diagnosis when ultrasound is not available. With the recent commercial development of relatively inexpensive, portable ultrasound imaging equipment, this technique of examination should become globally available in the immediate future.

The radiation exposure of an amniogram is unacceptable when a normal fetus is present, and that study poses the additional fetal hazards related to both amniocentesis and contrast agent use. Moreover, this method is not fully reliable prior to the 12 to 14-week stage of gestation. The authors refer to ultrasound as a "promising" technique (as of 1971) for the diagnosis of hydatidiform mole. Since that time, the instrumentation for (and collective experience with) obstetric ultrasound has so improved that it is now the most reliable, definitive diagnostic method for resolving the problem of suspected trophoblastic disease. Ultrasound is physically non-invasive, and with it, a diagnosis of mole can be established anytime after the first month of fetal life. This method also provides information about fetal vitality versus intrauterine fetal death, missed abortion or anembryonic pregnancy and will elucidate the differential choices pertinent to disproportionate uterine enlargement (namely, incorrect dating, multiple gestation, intrinsic fetal tumour, myometrial tumour, or polyhydramnios). A representative ultrasound image of a hydatidiform mole is appended (Fig. 1).

Yours, etc.,
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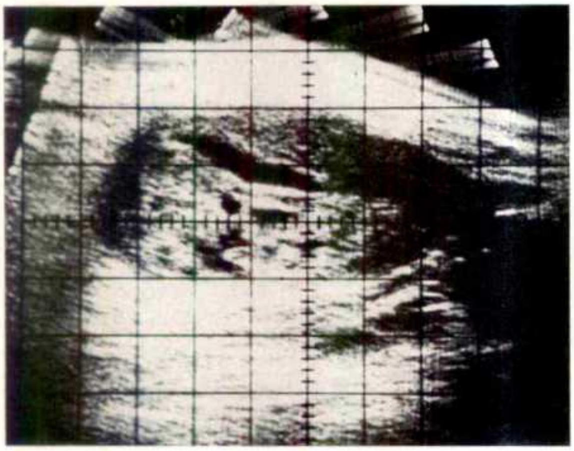

FIG. 1.

Longitudinal view showing an 14-week size uterus which is filled with placental tissue. Multiple haemorrhagic cysts are scattered throughout the mole.

THE EDITOR—SIR,

Amniography in the Early Diagnosis of Hydatidiform Mole

We have advocated amniography not as the procedure of choice in the diagnosis of hydatidiform mole but, to quote from our paper, as a "simple, safe and reliable alternative method" where ultrasound is not available. We therefore agree with Dr. Birnholz on the relative merits of these two techniques.

However, we do not share his optimism that ultrasound imaging equipment should become globally available in the immediate future, particularly in some of the developing countries. We feel that in these areas, including our own, it will be many years before ultrasound facilities become generally available outside the few large urban medical centres, and until then, amniography will continue to have its place in the investigation of suspected molar pregnancy.

Yours etc.,
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THE EDITOR—SIR,

Focal Spot Measurements

In a recent publication (Robinson and Grimshaw, 1975) a comparison was made of the pinhole and star-pattern methods of focal spot size determinations. The authors highlighted the practical difficulties associated with the pinhole technique and also the fact that this method does not take into account the effect on resolution of the focal spot intensity distribution. The star-pattern technique which could provide a quantitative measure of the radiographic properties of the focal spot was proposed as an alternative to the pinhole method.

Some of the objections to the pinhole method are no longer valid. Furthermore, this method has advantages when compared with the star-pattern technique which is itself not free from experimental difficulties. It should be noted that:

(1) By using rare-earth screens the pinhole exposure factors can be reduced. In fact using the fastest systems, up to ×6 magnified images of spots in the range 0·6–2·00 mm can be obtained using a single exposure. Up to ×12 magnification can be obtained with most overcouch tubes, without removing the light-beam diaphragm, in a period of a few minutes using multiple exposures. With this level of magnification, reasonably accurate size assessments can be performed especially if a travelling microscope is used.

(2) Pinhole photographs provide, routinely, valuable information concerning cathode geometry. Because the focal spot is essentially an electrostatic image of the filament structure, the pinhole picture is able to provide important information about distorted filaments.

Pictures showing a certain amount of lateral filament warping are routinely encountered, and since this warping must have occurred after the filament was mounted, some filament strain must be present. Other forms of distortion are observed, *e.g.* barrel-shaped images, produced by the filament bending out of the focusing cup, and trapezoidal focal-spot images produced by a slanting filament.

Since the factors producing these distortions may ultimately limit the tube life, regular pinhole photographs are a useful surveillance technique.

(3) Resolution techniques such as the star-pattern method are themselves subject to interpretive errors. Using visual assessment the point of visual contrast threshold must be used to determine the zero response point. The frequency at which there is zero response is a measure of the linespread function of the focal spot and is affected by its size and shape as well as its X-ray emission pattern. However, both shape and X-ray emission pattern also affect the point of visual contrast threshold. Hence in the star-pattern image of many focal spots the point of zero visual contrast will be different from the point of zero response. In fact without the presence of sharply-defined phase shifts in the star-pattern image the exact location of the zero response point can be difficult. This situation is analogous to that of locating the edges in a pinhole photograph, and raises similar experimental ambiguities.

Because the size and shape as well as the X-ray emission pattern affect the linespread, employing the disappearance frequency to calculate a focal spot size will usually give results which are larger or smaller than the actual physical dimensions (Robinson and Grimshaw, 1975). Moreover, it has been shown recently (Doi and Rossman, 1975) that for blood-vessel imaging using magnification angiography the actual physical dimensions of the focal spot rather than its intensity distribution probably define its imaging capability. In fact focal spot spatial frequency components which are detectable by means of a high contrast test pattern may not play any role in the clinical situation. Before determining focal spot sizes in terms of the disappearance frequency of a high contrast test pattern the relationship between visual quality of the radiographic image and focal spot size must be understood.

Because the pinhole and resolution techniques provide complementary information, focal spot assessment using both methods would be useful, whenever this is feasible.

Yours, etc.,
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THE EDITOR—SIR,

POSSIBLE APPLICATION OF A RADIOTHERAPY SIMULATOR FOR IMAGING OF BODY CROSS-SECTIONS

The development of computerized transaxial tomography has opened up new possibilities in radiotherapy, where a knowledge of cross sectional anatomy is of importance for treatment planning. Work has already been done in this context by Chernak *et al.* (1975). A technique for determining body cross sections for radiotherapy purposes based on Compton scattering has also been described by Farmer and Collins (1974).

Computerized scanning equipment, however, is very expensive. If we assume that a radiotherapy simulator will be available already in a radiotherapy department, then it would clearly be advantageous if cross sectional data could be obtained from this machine. We have studied this possibility, using the following method to derive cross sectional information with the aid of a digital computer.

The emergent X-ray beam is caused to form an image on a fluorescent screen, which is viewed by a high sensitivity television camera. Such a system has been described by Farmer and Ross (1975). For the present purpose the X-ray beam is collimated to a narrow fan of angle sufficient to encompass the patient, so that the camera output signal from a few adjoining T.V. lines represents the transmitted X-ray intensity through this section of the body. This video line signal can easily be digitized and stored in a computer. By rotating the gantry, further "projections" can be taken. The cross section can then be reconstructed using one of the now well known reconstruction algorithms (see, for example, Ramachandran and Lakshminarayanan, 1971). Similar work has been performed by Lanz *et al.* (1975), who have described a method of reconstructing cross sections of the heart using video data from standard fluoroscopy equipment.

Although this system is likely to be less sensitive than a commercial C.T. scanner, it nevertheless possesses several advantages:

1. Radiotherapy simulators are already present in most radiotherapy departments.
2. The mechanical movements necessary for cross sectional reconstruction (*i.e.* rotation about a point) are a feature of such machines.
3. It is theoretically possible to reconstruct several cross sections (perhaps simultaneously) by choosing a different video line or lines.
4. In addition to providing details of internal anatomy, a cross section would also provide the skin contour without recourse to a separate measurement.
5. The ability to determine many of the treatment parameters from a single machine would enable a more efficient use of time and space within a busy department and has obvious advantages for the patient.
6. Assuming that a simulator with this type of viewing system and a computer are available, the only extra cost is that of an interface between the two. The method is therefore potentially inexpensive, especially since computers are finding routine application in radiotherapy departments for performing other treatment planning calculations.

Work is currently in progress in Newcastle to implement the above design and evaluate its performance.

Yours, etc.,
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THE EDITOR—SIR,

ON THE COMPARISON OF DEPTH DOSE AND CELL-SURVIVAL CURVES

Dr. Kornelsen (Kornelsen and Young, 1975) was correct when he stated that the recognition of the similarity between percentage depth dose and cell-survival curves could lead to empirical equations which had an advantage over certain other empirical formulations. This was recognized by myself almost ten years ago (Glover, 1967a) when I developed an equation for percentage depth dose identical to his equation (2) except with λ for $1/Q$, and N for M. This was developed further (Glover, 1969) and resulted in a thesis (Glover, 1967b) in which the subject was thoroughly examined. The method has been applied to photon beams (Stovall and Wright, 1972) and fast neutrons (Smith *et al.*, 1974).

I am delighted that the method is proving useful and hope this rediscovery represents an improvement.

Yours, etc.,
J. R. GLOVER.

Monmouth Medical Center,
Long Branch, New Jersey 07740,
U.S.A.

REFERENCES

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THE EDITOR—SIR,

TIME FOR A REALIGNMENT OF PROFESSIONAL ASSOCIATIONS OF RADIOLOGISTS?

In commenting on the statement of co-operation issued by the British Institute of Radiology and the Royal College of Radiologists, Dr. Brindle (1976) claims that the logical conclusion is that they should amalgamate. My own logic, however, leads me to quite the opposite conclusion, and one which I am sure will be shared by all non-medical, and the majority of medical, members of the Institute.

The practice and advancement of medical science depend increasingly upon multi-disciplinary team-work, and nowhere more so than in those fields encompassed by the British Institute of Radiology. The evidence for this can be found in virtually any issue of this journal; but to rub the point home let me just mention the EMI-scanner, computerized planning in radiotherapy, radiopharmaceuticals, ultrasonics, etc., and ask, where would these be but for the work of the engineers, physicists, mathematicians, chemists and biologists who chose to take up the challenge of problems posed by their medical colleagues?

It is of course entirely proper that there should be separate bodies to safeguard the differing professional interests of individuals. Physicists have the Hospital Physicists' Association; chemists like myself have the Royal Institute of Chemistry; radiologists have their Royal College, and so on. The British Institute of Radiology is unique, however, in providing—as Dr. Brindle concedes—a forum in which members of all these different professions may meet on equal terms, and this must not be underrated.

In other countries, the nearest approach to an equivalent forum is provided by societies of nuclear medicine. The British Nuclear Medicine Society, however, is unique amongst such societies in restricting membership to the medically qualified, and in any case has a much narrower range of interest than the B.I.R.

Much of Dr. Brindle's letter is concerned with arguing a case for a split, within the Royal College of Radiologists, between diagnostic radiologists and radiotherapists. This, of course, is an internal affair of the College, and as such is no concern of mine, but I would suggest that there is no need to drag the B.I.R. into the controversy either. Rather, the Institute should continue to keep both parties aware of the common scientific ground between them.

Finally, if at the end of the day, change has to be forced upon us, let it be one which results from recognition of the ever widening role of the natural sciences in medicine. Thus, possibly in another generation or two, the B.I.R. should become the British Institute of Medical Science, and this Journal the B.J.M.S.

Yours, etc.,
D. J. SILVESTER.

M.R.C. Cyclotron Unit,
Hammersmith Hospital,
Ducane Road,
London, W.12.

REFERENCE

BRINDLE, M. J., 1976. Time for a realignment of professional associations of radiologists. *British Journal of Radiology*, *49*, 478–479.

THE EDITOR—SIR,

THE B.I.R. AND THE ROYAL COLLEGE

Dr. Brindle in his interesting letter has raised two issues which are in fact only vaguely connected; the relationship between the B.I.R. and the Royal College is one issue, the relationship between radiotherapy and radiodiagnosis is another.

It is the first nettle that I wish to grasp. Dr. Brindle asks (as many other have done) why, when they have gone so far in their co-operation, the Royal College of Radiologists and the British Institute of Radiology cannot actually amalgamate. I myself asked the same question when, several years ago, I began to hope for opportunities for the two organizations to grow closer together in sharing their joint work. It is as a result of the similar wishes of both medical and non-medical members active in the affairs of the B.I.R. and the Royal College (and previously the Faculty) that the present closer cooperation has developed. Most of these members however, who are deeply involved in the work of the two organizations, have seen that the British Institute of Radiology and the Royal College of Radiologists are essentially different and both are required.

Let me quote Dr. Brindle's own words. "An amalgamation would exclude non-medical members, but of course an equivalent forum could be provided by meetings between the combined association and a special section of an established society or a new non-medical group formed for the purpose".

The point is that it is true, as he indicates (though I think the word "exclude" is too strong), that in an amalgamated body with the Royal College the non-medical scientists could not be on quite the same footing. The inescapable inference is that if such a thing ever happened the B.I.R. itself would have to be re-invented complete with a very substantial number of medical members. Neither an established nor a new non-medical group would serve the purpose of this essentially interdisciplinary learned society.

If one does not really know what the B.I.R. does, it is easy to think that the public meetings of non-medical and medical members (and their guests) are the major substance of collaboration. They are, however, only the tip of the iceberg. Nor, even, is the journal the centre of the life of the B.I.R. The Institute's chief work is carried out by committees which create working parties to study jointly, with medical and non-medical members on a basis of complete equality, a multitude of scientific problems concerned with the changing practice of "radiology". Furthermore, the Institute (known all over the world for its work) is represented on many national and international scientific bodies in a way which gives the medical profession an equal voice with the non-medical. These committees and working parties go on month in month out. *They* are the forum where matters of mutual concern are really thrashed out as they can only be between equals. The very essence of the B.I.R. is equality of voice and vote between scientists of different kinds. The essential nature of the Royal College of Radiologists, on the other hand, is to be a professional body concerned not only with the scientific side of radiology but with clinical responsibility for the patient, something which derives its justification from medical training and examination. The Royal College can and does consult and value non-medical scientists, but it cannot place the non-medical and the medical scientist on an identical footing in its committee structures. Amalgamation would destroy the present B.I.R. and, if I may repeat myself, it would then have to be reinvented because medical radiologists need such a society.

The recent history of the B.I.R. has been one of vigorous growth and change. The exigencies of economic reality and discourse with the Royal College about sharing facilities seem to have brought home to both organizations what their roles should be. From a farily intimate knowledge of the B.I.R. I am inclined to think that at least half of its liveliness comes from the non-medical members and that its broad based and flexible constitution is very appropriately matched with the developing pattern of medicine.

It is also very important for the B.I.R. to provide services which the diagnostic radiologists, who form such a large part of the membership, recognize as being useful to them. This is much easier when members write or speak about their problems and wishes and I would like to take the opportunity of asking them to do so, remembering, of course that the B.I.R. is concerned with all medical and scientific aspects of radiology in its broadest sense, but not with such matters as salaries and professional qualifications.

Yours, etc.,
G. H. DUBOULAY.

Lysholm Radiological Department,
The National Hospital,
Queen Square,
London WC1N 3BG.

THE EDITOR—SIR,

TERMINOLOGY IN COMPUTERIZED IMAGING

Dr. J. P. Nicholson appealed in July's journal for improved terminology in computerized scanning. I should like to support this.

While great credit must go to E.M.I. for pioneering this valuable new X-ray system, other firms are manufacturing comparable apparatus, and it is unlikely the name EMI scanning will be acceptable on a wide basis. The term computerized tomographic scanning has been used for the radioisotope procedure developed by Professor Mallard and his team at Aberdeen, and CT scanning is sometimes used for the X-ray procedure, and there is a serious risk of confusion unless suitable agreed names be found. The British Institute of Radiology, being a multi-disciplinary body, is perhaps the best equipped in the world to resolve this question.

We need both for the X-ray and radioisotope system a noun and a verb. We need to refer to a "computer X-ray tomographic scan", and to arrange for a patient to be "computer X-ray tomographically scanned", and similarly for the radioisotope procedures. The names must be brief, and above all they must be clear and unambiguous.

I therefore endorse the suggestion that readers be invited to put forward recommendations to the Institute, and hope Council will shortly have the pleasure of choosing names for these two very healthy and robust young babies.

Yours etc.
F. T. FARMER.

Regional Medical Physics Department,
Newcastl General Hospital,
Newcasle upon Tyne.

1976, *British Journal of Radiology*, *49*, 816

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements in the *BIR BULLETIN* which is distributed quarterly to all members.

David Anderson-Berry Prize

A David Anderson-Berry silver-gilt medal, together with a sum of money amounting to not less than £100 (£100 = U.S. $200), will be awarded by the Council of the Royal Society of Edinburgh during 1976. The prize will be awarded for recent work on the effects of X rays and other forms of radiation on living tissues. Published work will be taken into consideration if submitted to the Society with the application.

In addition to direct application for the prize, proposals may be made on behalf of others.

Applications and proposals must be in the hands of the General Secretary, Royal Society of Edinburgh, 22/24 George Street, Edinburgh 2PQ, Scotland, not later than September 28, 1976.

British Vacuum Council Prize Award

The British Vacuum Council offers a prize of £100 for a paper based on a postgraduate research thesis in vacuum or a related topic in which vacuum science and/or engineering is of major importance. The research in question must be carried out in a laboratory in the United Kingdom.

Papers submitted as entries for the British Vacuum Council prize must not previously have been published elsewhere. Entries for the 1976 prize must be submitted not later than November 1 to the address shown below, from which further details are available. The Secretary, British Vacuum Council, 47 Belgrave Square, London SW1X 8QX.

Joint Radiological Meeting in Leeds

Sponsored by The Royal College of Radiologists and The British Institute of Radiology. To be held September 24–25, 1976. Registration and information from the General Secretary, B.I.R., 32 Welbeck Street, London W1M 7PG.

A Symposium on Radioisotopes in Cardiology

Jointly organized by The British Institute of Radiology and the British Cardiac Society will be held on Wednesday, September 29, 1976, at the Greenwood Conference Centre, Guy's Hospital.

Registration fee: £9·50 including lunch, morning coffee and afternoon tea.

Further details and registration forms will be available from The Secretary, British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Attendance may be limited and registrations will be accepted in the order they are received.

European Symposium on Gynaecological Cancer

This meeting to be held at the Hilton Hotel, Athens, on October 7–8, 1976 under the auspices of the European Association of Radiology.

Further information from: EAR Symposium on Gynaecological Cancer, Aireteion Hospital, 76V as. Sophias Avenue, Athens 611, Greece.

8th Congress of the Society of Hungarian Radiologists and 12th Annual Meeting of the European Society for Radiation Biology

To be held in Budapest, Hungary, October 19–22, 1976.

For further information please contact the Congress Office (H-1361 Budapest, PO Box 32, Hungary).

Autumn Meeting North of England Branch of B.I.R.

The autumn meeting of the North of England Branch of The British Institute of Radiology will be held at the Children's Hospital, Sheffield, on Saturday, October 30.

This is the Centenary year of the Children's Hospital and the staff will be presenting short papers. If any member fails to receive a notice of this meeting by post would they please inform the General Secretary of the B.I.R.

British Medical Ultrasonics Group

The Annual Meeting of the British Medical Ultrasonics Group will be held in Dundee on December 20–21, 1976.

Papers will be presented on all aspects of diagnostic ultrasound and there will be an associated commercial exhibition.

Further details from: The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiation Protection: An Example of Action Against Modern Hazards

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical application of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colegio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

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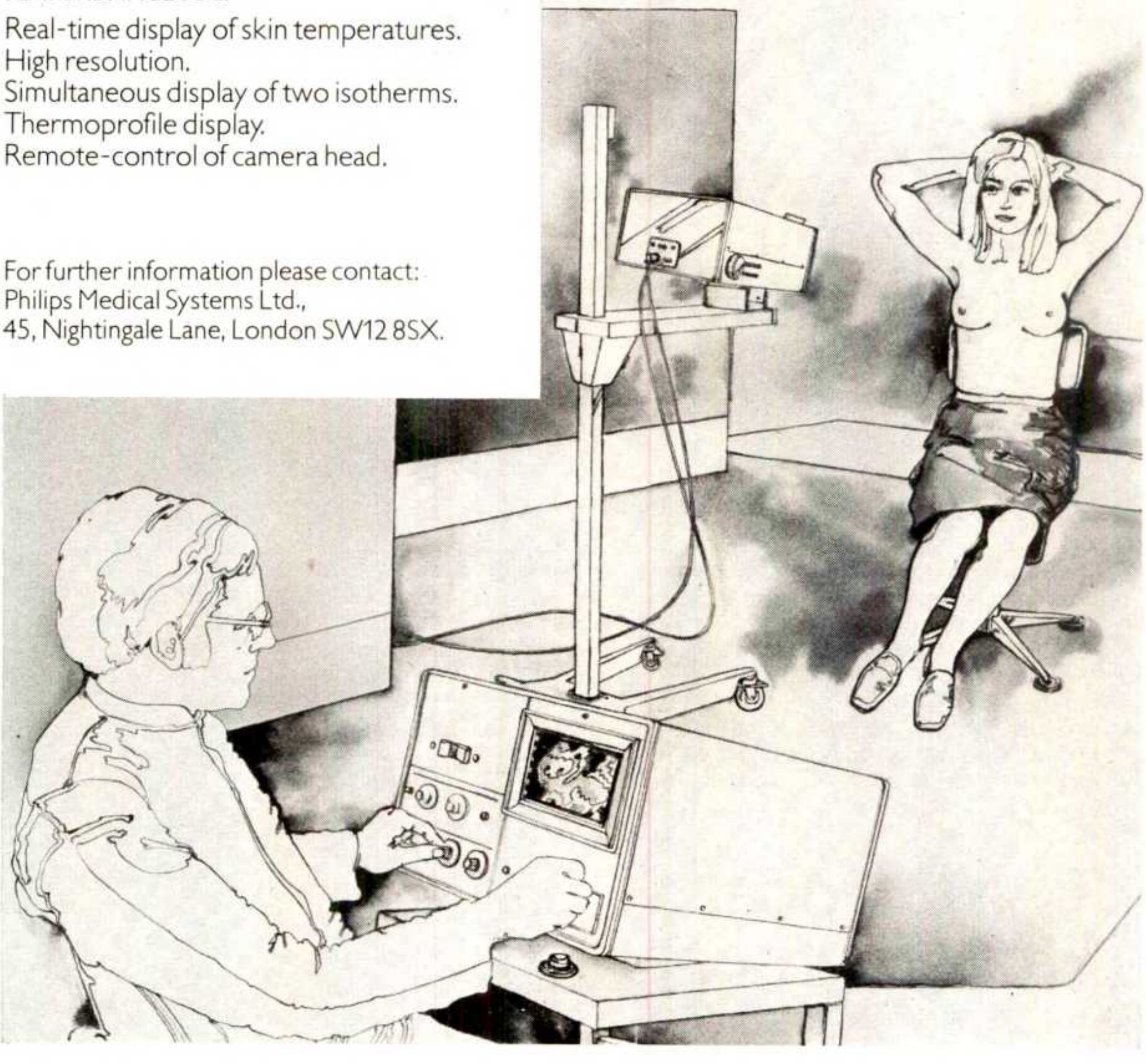

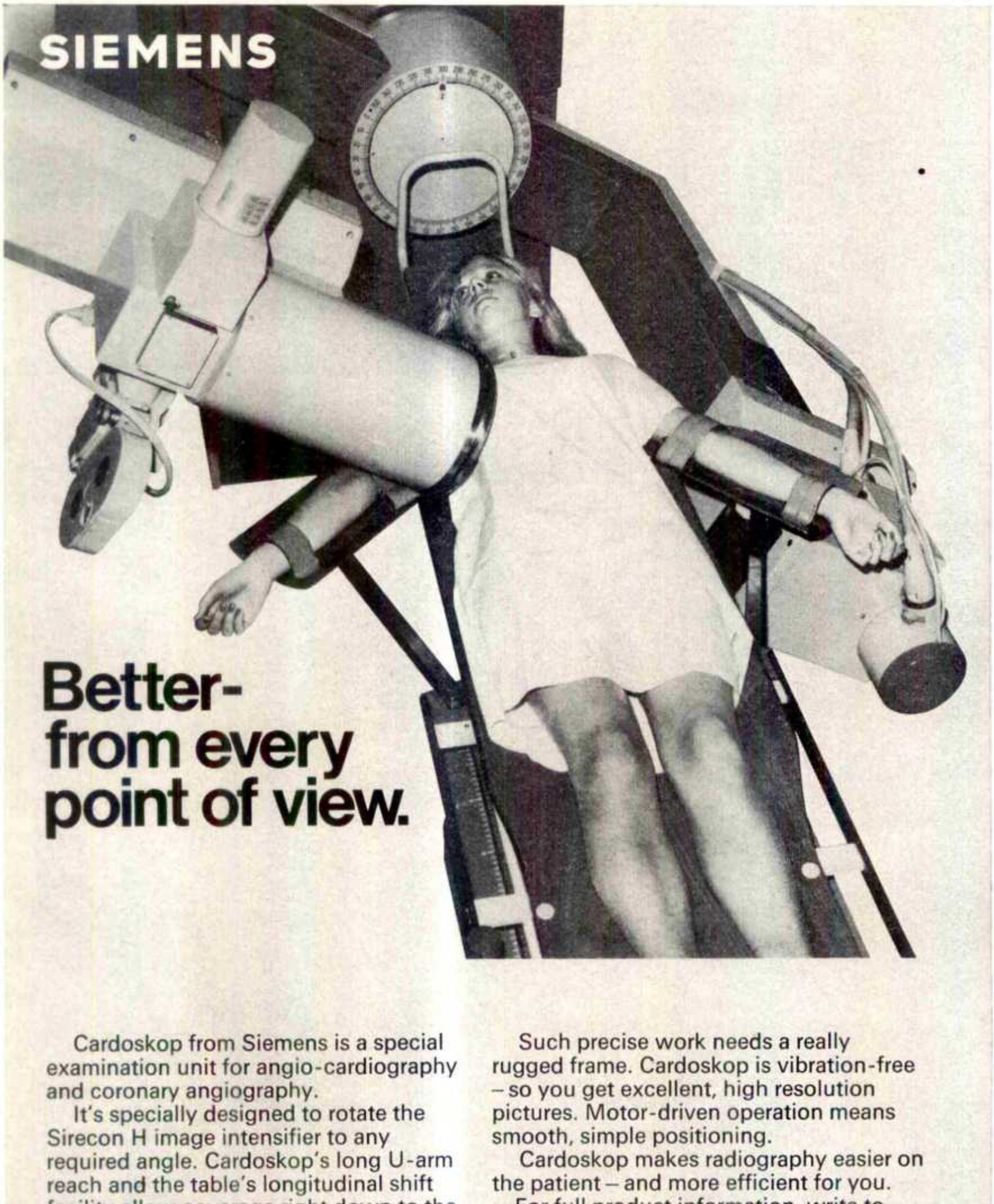

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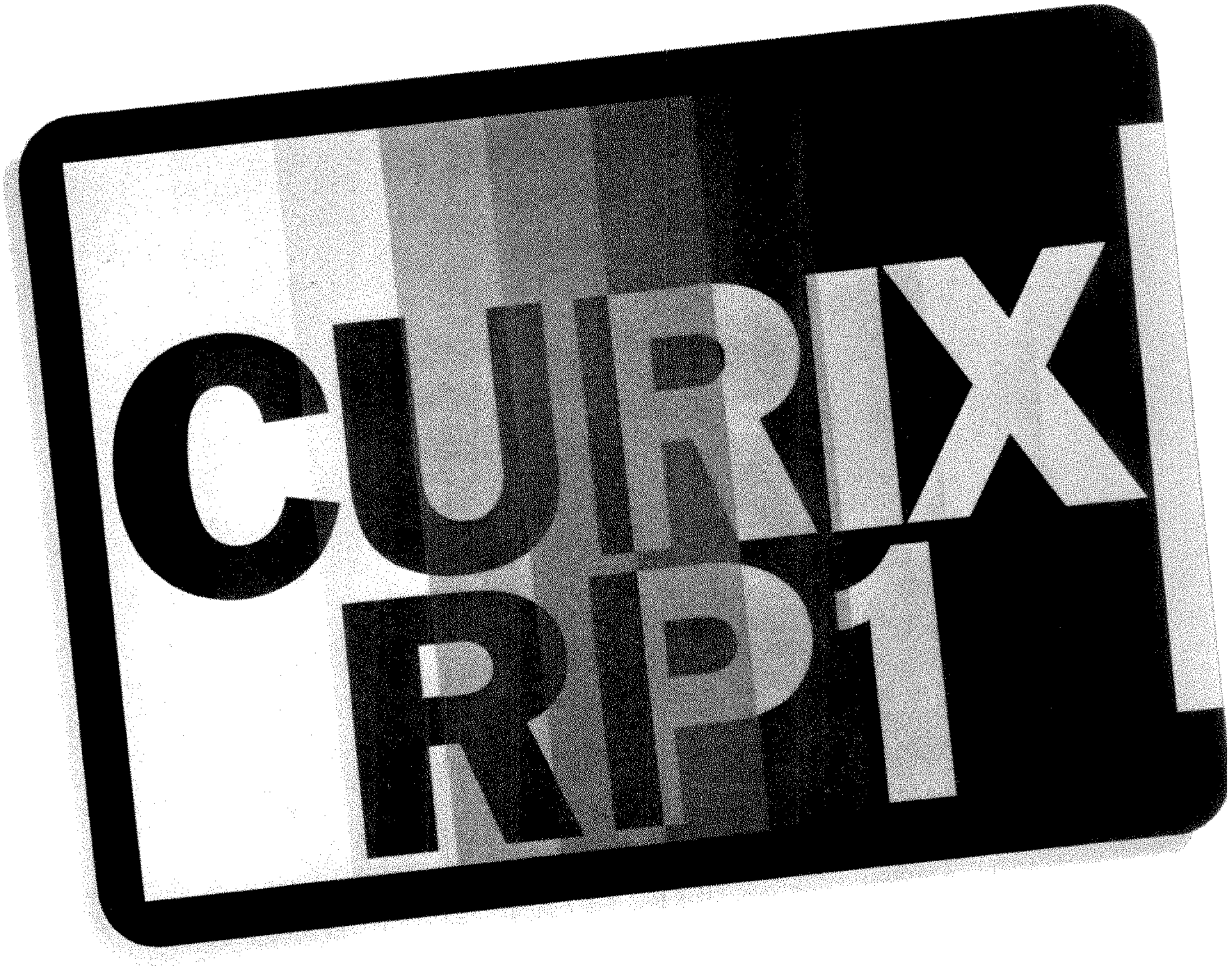

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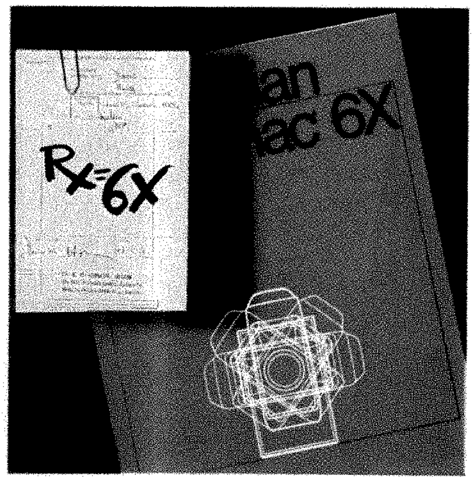

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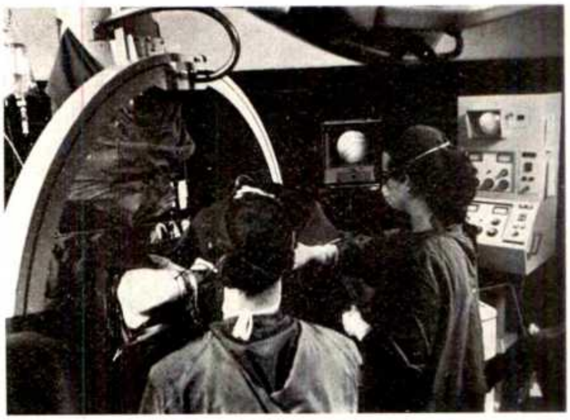

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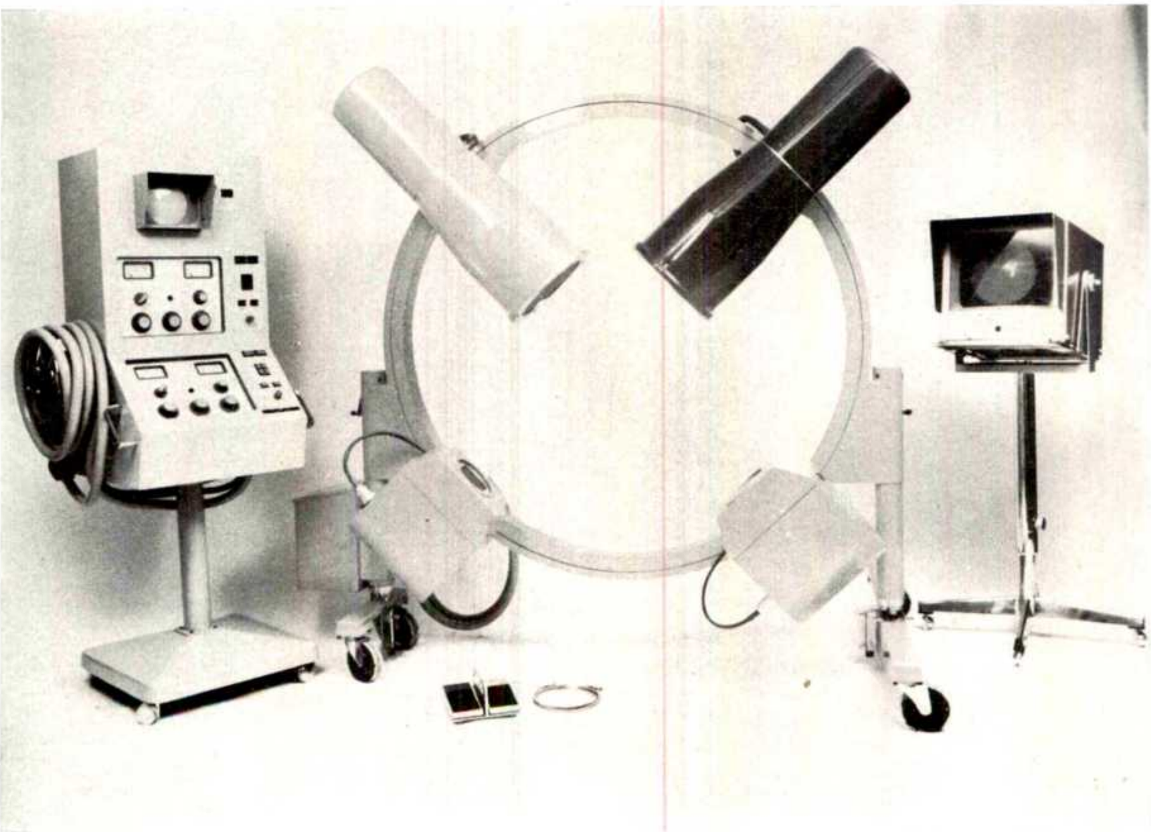

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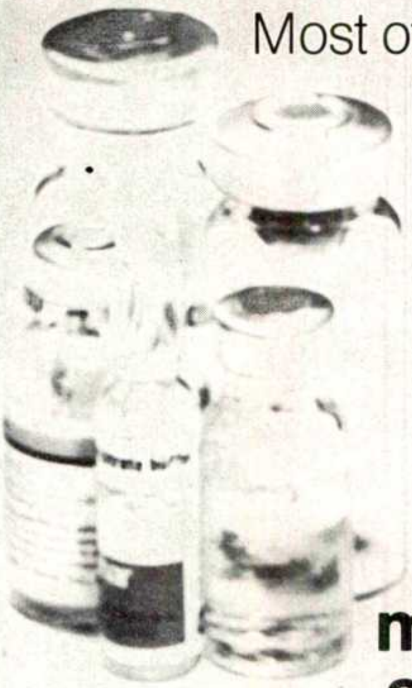

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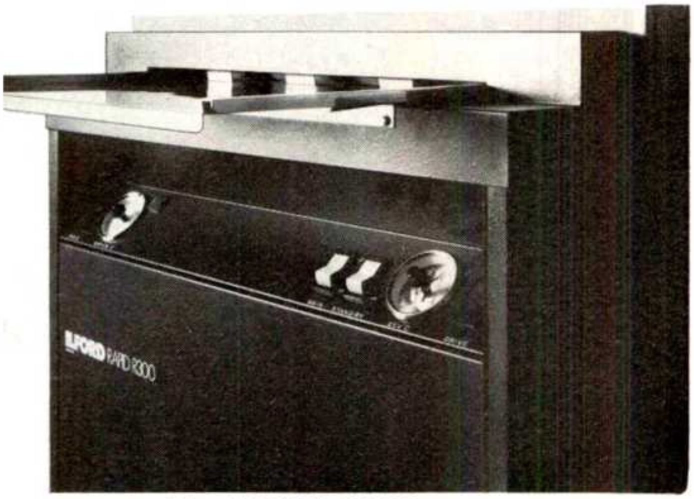

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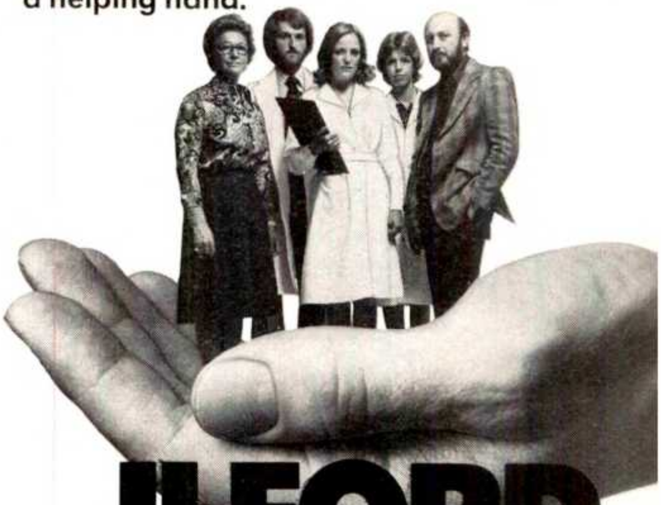

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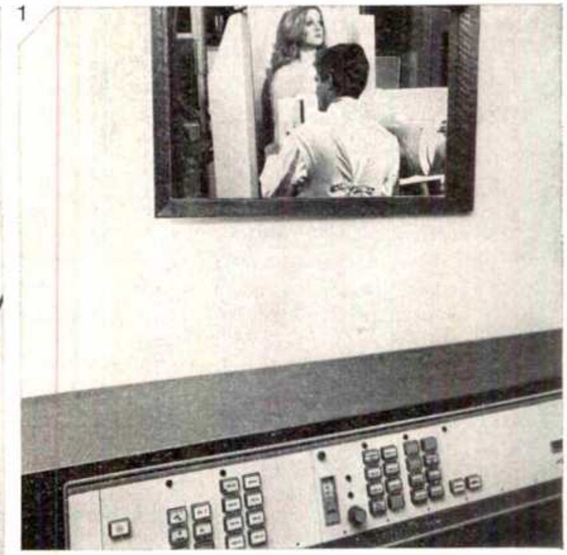

Photographs by courtesy of Rijnoord Hospital, Alphen a.d. Rijn, The Netherlands.

1. All controls are, of course, duplicated on the generator desk.

2. For bucky work on the DIAGNOST 73, or an additional unit, the generator desk incorporates additional controls for anatomically programmed radiography. You are free to distribute the settings you require over the available push-buttons in whatever way you like.

3. The generators incorporate automatic kV and mA control ensuring bright, evenly illuminated fluoroscopy pictures. If necessary, you can override the automatic settings for special fluoroscopic techniques.

2

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R. F. MOULD *Foreword by Professor Sir David Smithers*

An introduction to medical statistics for those studying for MB, BS, MRCP and FRCR examinations, and for all those members of the medical profession who wish to have a basic grounding in statistics. The particular features of this book are: 1 – the emphasis placed on introductory sections prior to practical applications of statistical techniques; 2 – a minimum of mathematics; 3 – the numbers used in worked examples are simple integers whenever possible; 4 – a high ratio of diagrams to text; 5 – an attractive and practical page layout; 6 – examples are drawn from a wide medical spectrum; 7 – a good classified index; 8 – the book is short. The final two chapters are particularly elegant and are devoted to survival rate calculations and clinical trials. They are particularly relevant for oncologists sitting for the FRCR.

100 pages (large format) Illustrated Cased £4·00 net

RADIOLOGIST

PRINCESS ALEXANDRA HOSPITAL

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Applications are invited from Registered Medical Practitioners with specialist qualfications for the position of Radiologist, Department of Diagnostic Radiology, Princess Alexandra Hospital.

Salary—$23,606—$29,458 per annum depending on experience.

Annual Leave is five weeks per annum and conference leave is available on application to the Board. Study leave is available after seven years' service. This may be taken as six months on full pay or three months on full pay with additional sums to cover air-line tickets and living expenses during the period.

The Hospital is one of three teaching hospitals associated with the University of Queensland. All specialities except obstetrics and paediatrics are represented and the successful applicant would have the opportunity to develop an interest in the radiology of any of the specialities represented. A computerized Axial Tomography Unit is about to be installed.

In 1974–75, the Department of Diagnostic Radiology performed 89,304 examinations including 9,866 procedures.

Any further particulars can be obtained by contacting the Director of Diagnostic Radiology.

Applications giving details of qualifications, age and experience together with the names of three referees, should reach the Medical Superintendent, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, 4102 (6959).

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At last, a 5MV linear accelerator that's good enough for the Philips integrated therapy programme.

The Philips Integrated Therapy Programme ensures increased efficiency in the modern radiotherapy department by having a common design philosophy, similarity of operational procedures and simplified service.

The programme embodies maximum reliability and patient safety. It incorporates a long-term plan providing the clinic and hospital with the essential equipment for today and the future.

The new Philips 5MV linear accelerator is the latest introduction to the Programme.

A machine that has been specifically designed for the radiotherapy department needing a unit for X-ray treatments when electron therapy is not required.

Fulfilling an important role.

For the smaller clinic, the SL.75/5 offers all the sophistication of the higher energy linear accelerators in the same series, but it has also been carefully designed to match other units in the 4–6MV range.

For departments where the higher energy machines are already in operation, the common design philosophy of the 5MV enables it to be readily integrated into the department.

All this makes the 5MV ideal as a primary treatment unit or a secondary unit for the larger overworked clinic.

This is what you can expect in performance.

The SL.75/5 will handle 60 patients a day.

The X-ray energy can be set in the 4–6MV range and is monitored and controlled by the same system that is used in the other Philips linear accelerators and so ensures accurate energy stability.

Dose rates at 350 rads per minute at one metre can be achieved at 5MV. (Equivalent to 550 rads per minute at 80cm.)

The maximum field size is 40x40cm at one metre F.S.D.

A 420° gantry rotation has been included to ensure rapid setting up of patient treatments.

All movements are motorised with variable speed control and have simultaneous movement capabilities.

There is also a choice of treatment tables. Either a high lift ram type or an above floor version. (A combination of table side supports and centre spine construction allows beam access from any angle.)

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A major aspect of the SL.75/5 design concerned safety.

The dual channel dosimetry system is backed by a timer. Select and confirm routines ensure maximum patient safety and reduce operational errors. And if required, a verification system can also be added.

Where room protection is limited, a retractable beam absorber is available that can be interlocked to prevent irradiation to unsafe directions.

Dose and time LED displays are automatically maintained in the event of an electrical supply failure.

Find out more about the 5MV and the entire Philips Integrated Therapy Programme.

Here we have made a brief mention of just a few aspects that make the SL.75/5 an important addition to the Philips Integrated Therapy Programme.

The entire Programme includes cobalt units, localiser/simulator, a treatment planning system and ortho-voltage therapy units.

Philips are constantly developing new equipment for the highly specialised radiotherapy field.

If you would like to know more about the Philips Integrated Therapy Programme,
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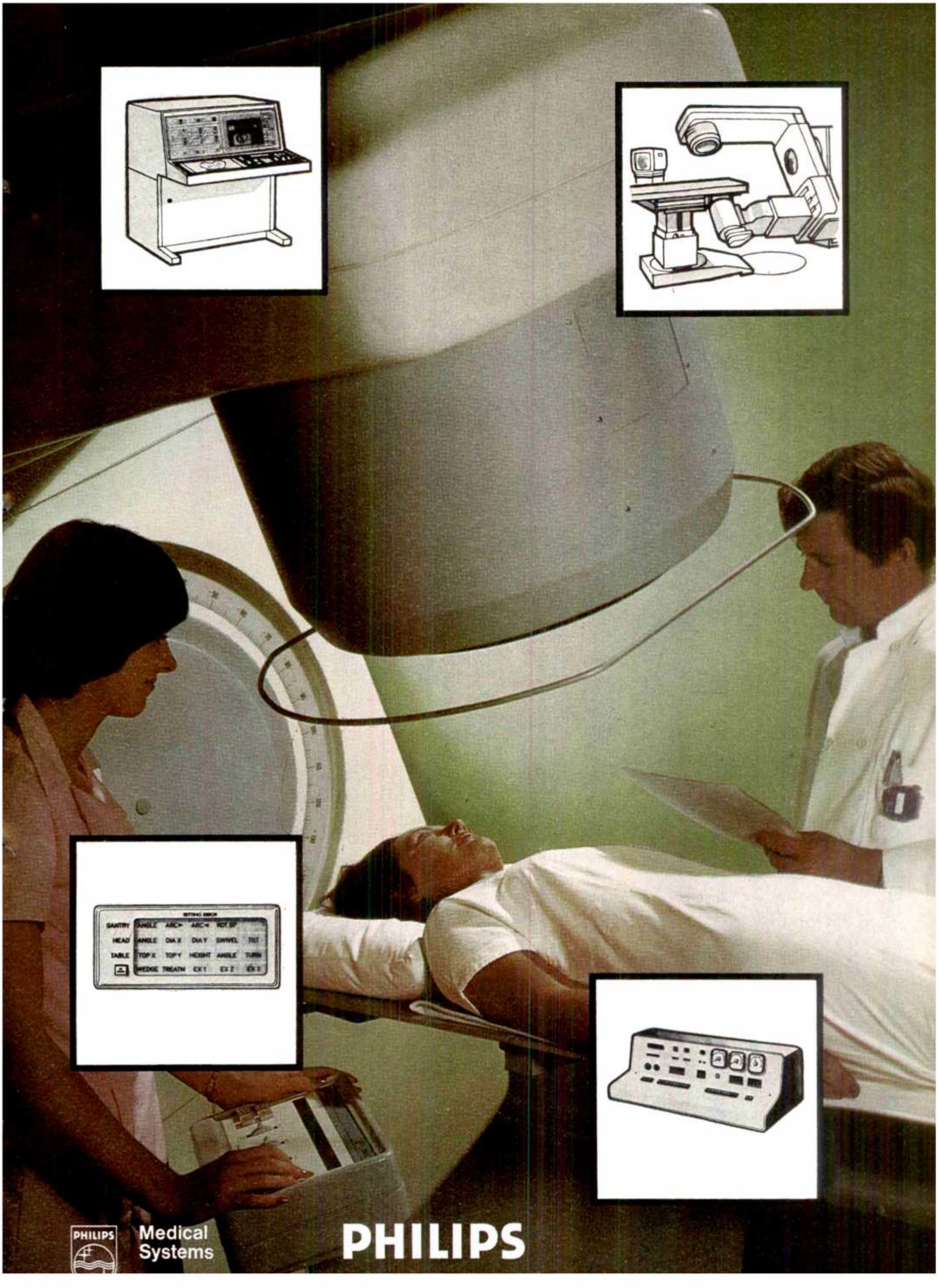
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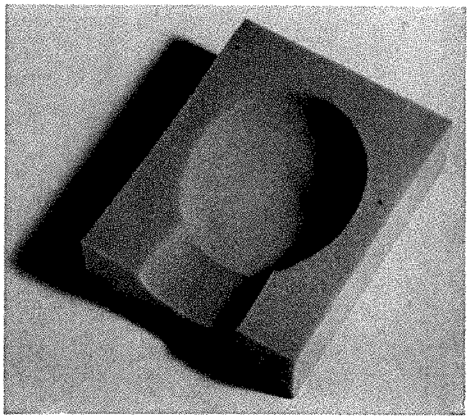

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It is expected that the successful applicant would be offered an honorary Consultants contract. Salary £7,536–£10,689 (four increments). A pay supplement of £312 is applicable at the minimum point of the scale.

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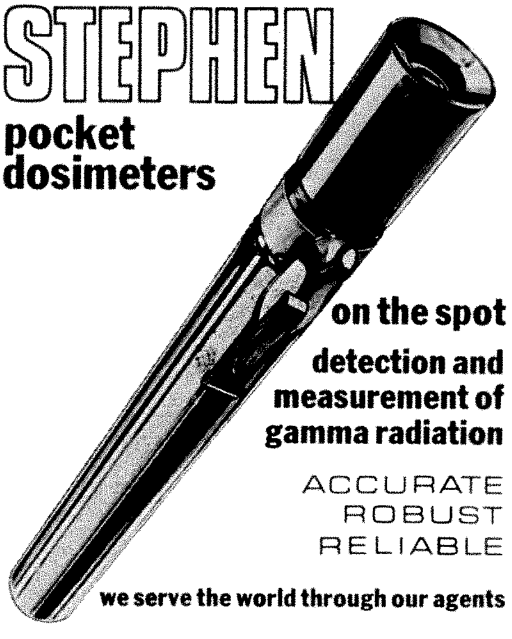

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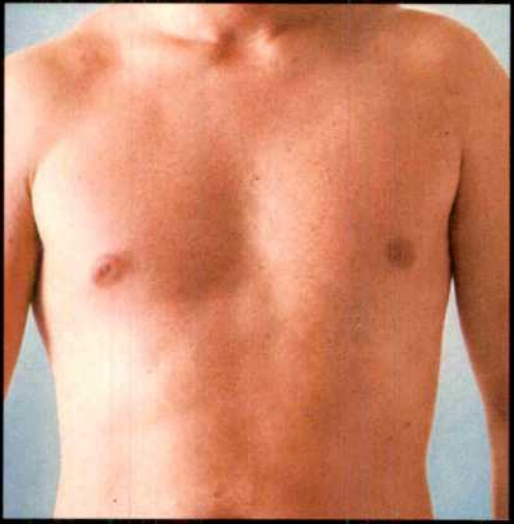

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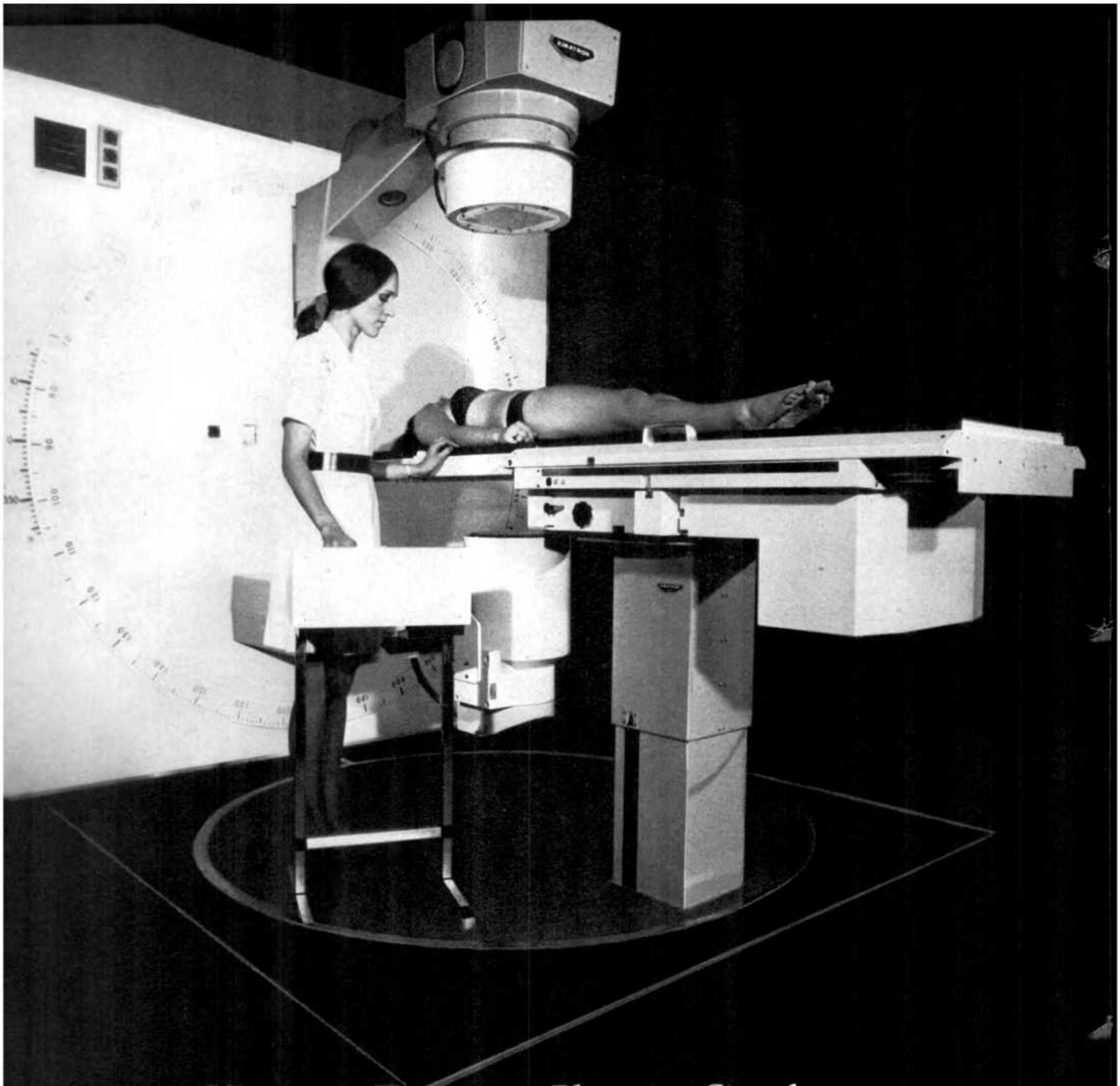

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For further information and details please write to:

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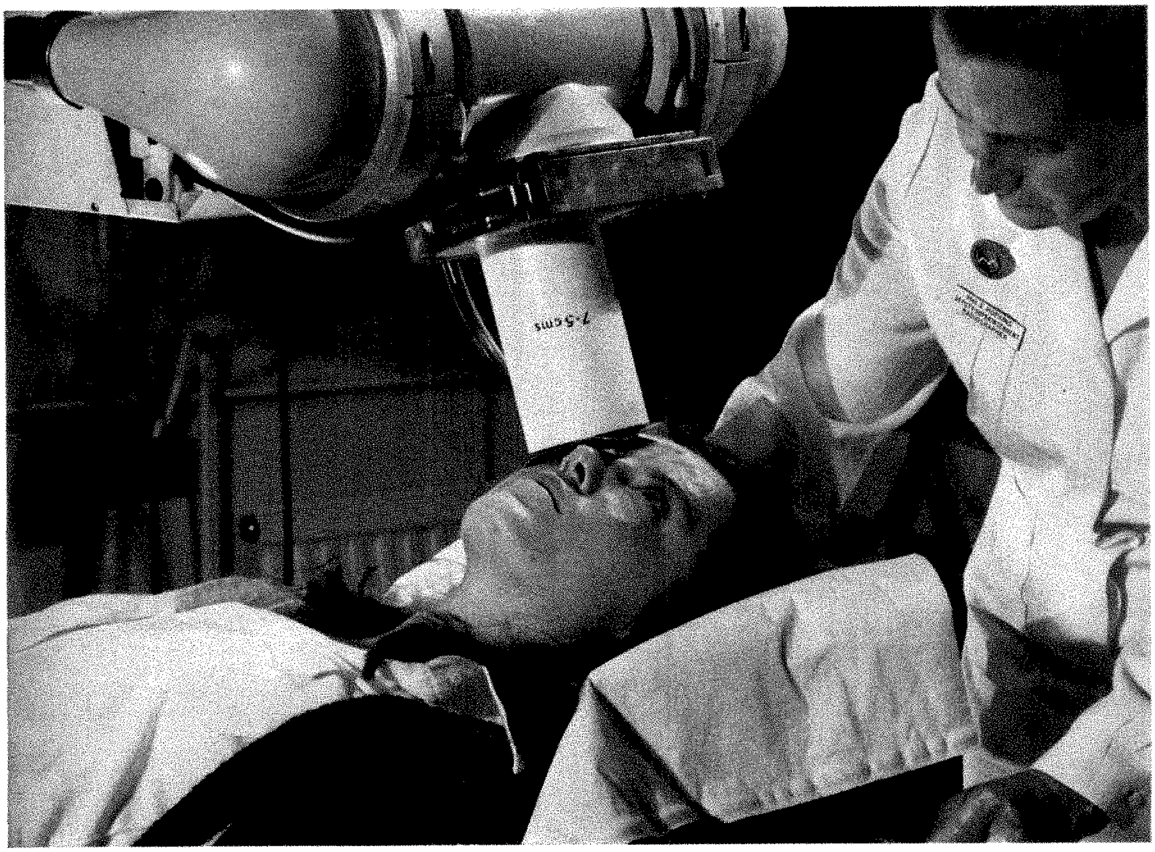

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Hammersmith Hospital

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25—26 November 1976

This course is intended as an introduction to organ scanning stressing its clinical implications. It will include practical demonstrations of the uses of gamma cameras, scanners, and the preparation of radiopharmaceuticals.

Course organizer: Dr. J. P. Lavender

Fee: £25 (including lunch)

Further details and application forms from:

The Deputy Secretary's Office, Royal Postgraduate Medical School, Hammersmith Hospital, Du Cane Road, London W12 0HS. Tel. 01–743 2030, ext. 351.

There is a limited number of places available and early applications are requested.

The Royal College
of Radiologists

Final Fellowship Examination—Radiodiagnosis

Nairobi, Kenya—October 1977

A Final Fellowship Examination (in Radiodiagnosis only) of The Royal College of Radiologists will be held in Nairobi, Kenya, in October 1977. To be eligible to take this examination candidates must have held for at least two years a radiological qualification recognized by The Royal College of Radiolgists; or have trained for three years in a recognized department, during which time candidates must have obtained the First Examination for the Fellowship.

The written papers will be held on 3rd and 4th October, 1977, and the oral examinations will commence on 24th October, 1977. The closing date for applications is 13th June, 1977, and applications received after this date cannot be accepted.

Further information and application forms can be obtained from The Examinations Secretary, The Royal College of Radiologists, 28 Portland Place, London, W1N 4DE.

Dr. L. Reynolds Associates, P.C.
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Invites applications for the position of

Staff Radiotherapist

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The Hospital has an out-patient and in-patient services, over 1000 beds, and full diagnostic facilities. The Radiation Therapy Department includes 6 Mev Linac and Cobalt 60 teletherapy, to give the appropriate support modalities.

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A.R.R.T. registered or eligible. Large Midwestern University – affiliated radiation therapy division. Equipment includes simulator, cobalt, betatron, superficial, linear accelerator. Physics and Dosimetry support. Excellent fringe benefits including a retirement program. Salary commensurate with qualifications and experience. Please direct enquiries to:

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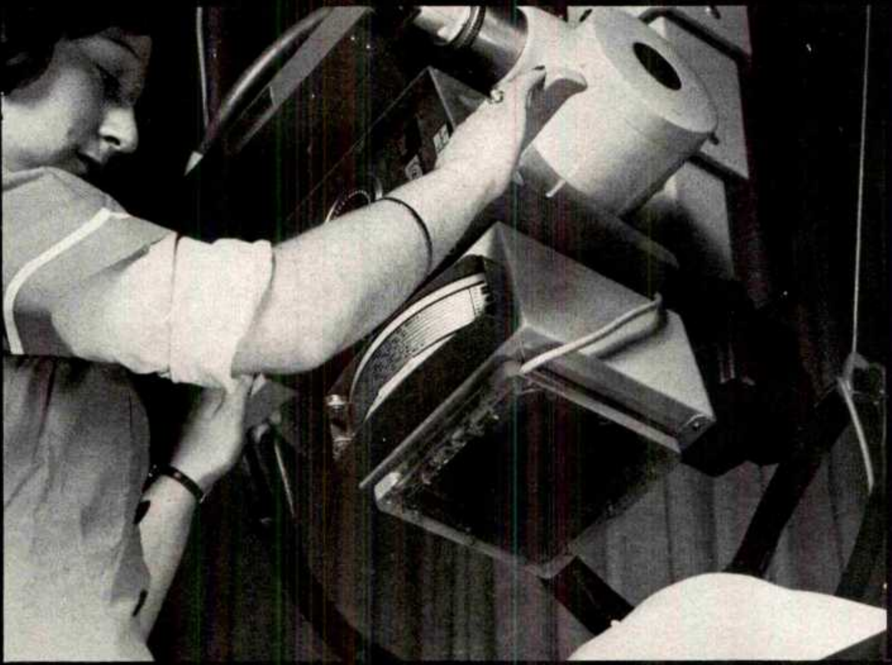

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Candidates should have Part I F.R.C.R. or have fulfilled the requirements for it.

Further information from Professor J. P. Murray Regional Hospital, Galway (Tel. (091) – 64141) and applications, with names of two referees, to Personnel Officer, Western Health Board, Merlin Park Regional Hospital, Galway,

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URO-RADIOLOGY WEEKEND

10th and 11th December 1976

in the Lecture Theatre, Institute of Urology,
172 Shaftesbury Avenue, London WC2H 8JE

FRIDAY 10th DECEMBER		
2.15–2.45 p.m.	Differential diagnosis of chronic pyelonephritis	Dr. T. Sherwood
3.00–3.30	Ultrasound–advances and outlook	Dr. H. B. Meire
3.45	TEA	
4.15–4.50	Radiologists' guide to the bladder 1976	Mr. P. H. L. Worth
5.00	Unknown cases presented to:	Dr. I. Kelsey Fry and Dr. H. M. Saxton
	Pathologist:	Dr. R. C. B. Pugh
6.15	Sherry	
SATURDAY 11th DECEMBER		
9.30–10.00 a.m.	Prostatic carcinoma–bone scans and lymphograms	Mr. E. P. N. O'Donoghue
10.15–10.45	Contrast media for angiography	Dr. P. Armstrong
11.00	COFFEE	
11.30	*Discussion: Better management in radiology* *Part 1:* See and learn more on X-rays *Part 2:* The radiology department	Dr. T. Sherwood Dr. H. M. Saxton
1.15 p.m.	LUNCH	
2.30	Diagnosis of upper urinary tract obstruction *Discussion–Chairman* with:	Mr. G. D. Chisholm Dr. C. D. R. Flower Mr. R. H. Whitaker Mr. H. N. Whitfield
4.00	TEA	

Fee: £14 (including coffee, lunch and tea)

Applications to the Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE.

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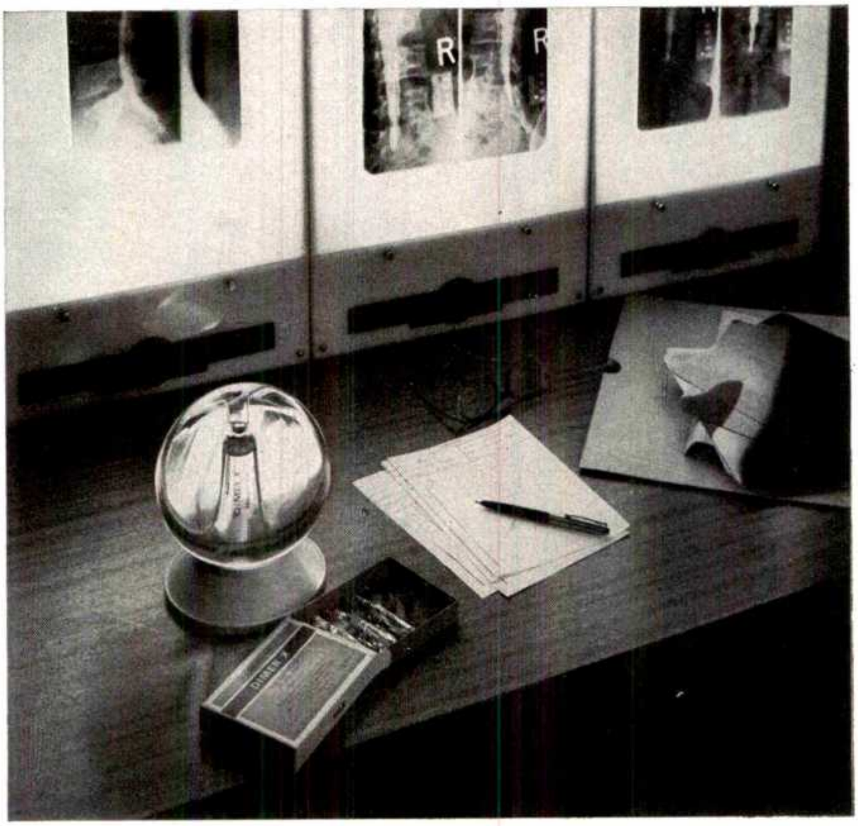

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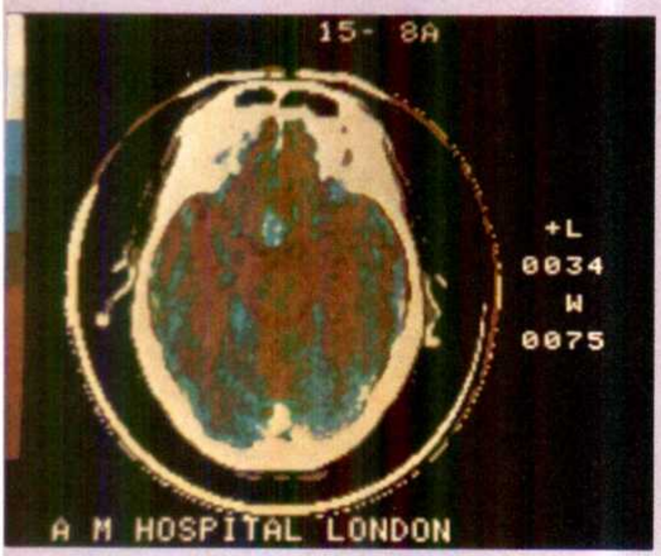

Patient Code 15, 8A.

Patient suffering from hypopituitrism. The EMI-scan shows a pituitary adenoma. The scan, taken after the injection of contrast, clearly shows the suprasellar extension into the chiasmatic cistern.

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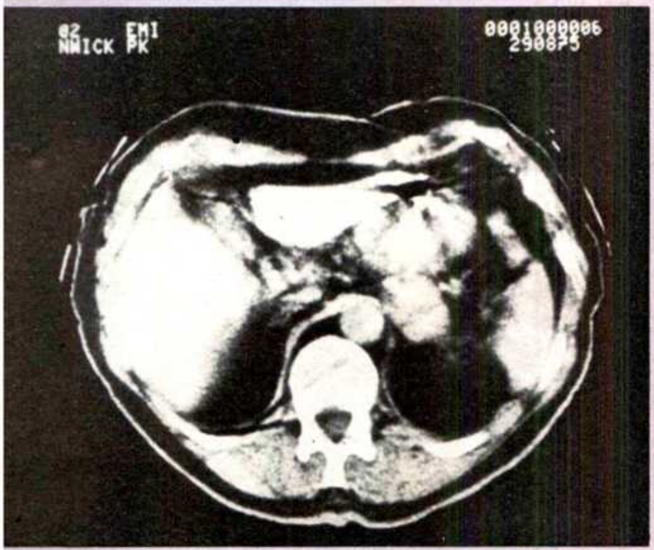
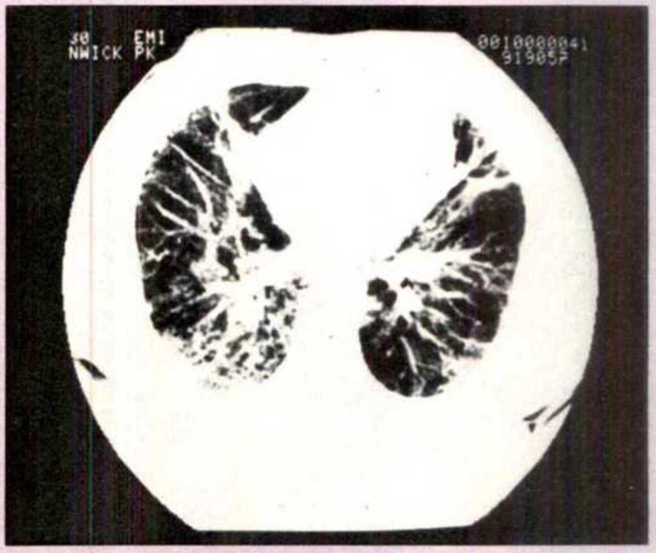
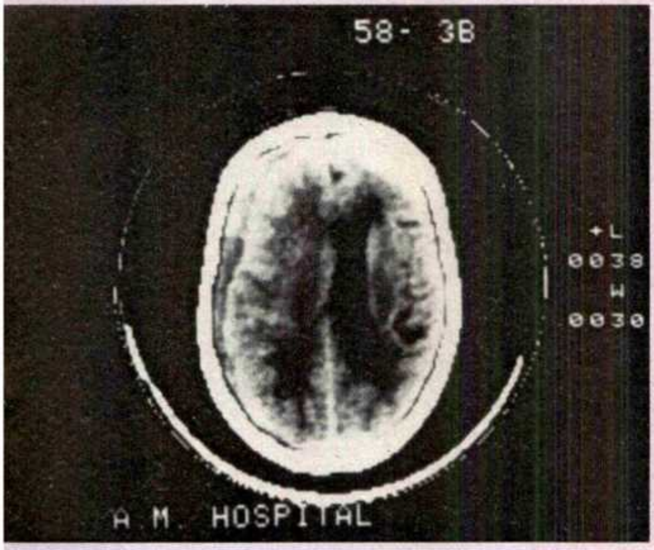


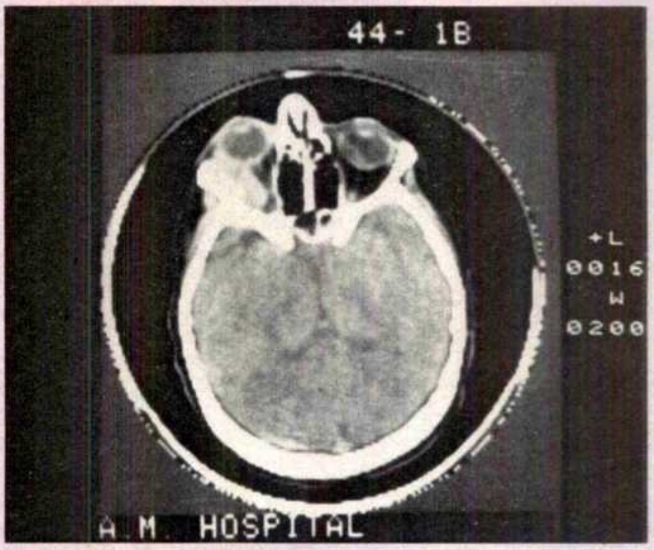
Scan 02.
Scan through 1st lumbar vertebra, demonstrates pancreatic cyst.



Scan 30.
This scan clearly demonstrates interstitial fibrosis in the lungs. Due to the short scan time of the CT5005, the patient was able to suspend respiration for the duration of the scan, thus allowing the lung vessels to be clearly demonstrated without blurring.



Patient Code 58, 3B.
79 year old female with a history of two falls in the month previous to admission. She was admitted in a confused and drowsy state. The EMI-scan clearly demonstrates a left subdural haematoma.
Note: Scan taken in "high sensitivity" mode. Note the clear delineation between grey and white matter.



Patient Code 44, 1B.
Young male patient with a 12 month history of increasing proptosis and limitation of lateral occular movements. Lately he has suffered from conjunctival oedema. The EMI-scan demonstrates a mass in the lateral section of the left orbit, with early calcification visible within the mass. Note the detail visible in the orbital regions.

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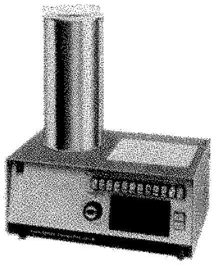

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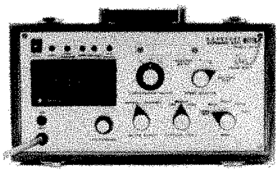

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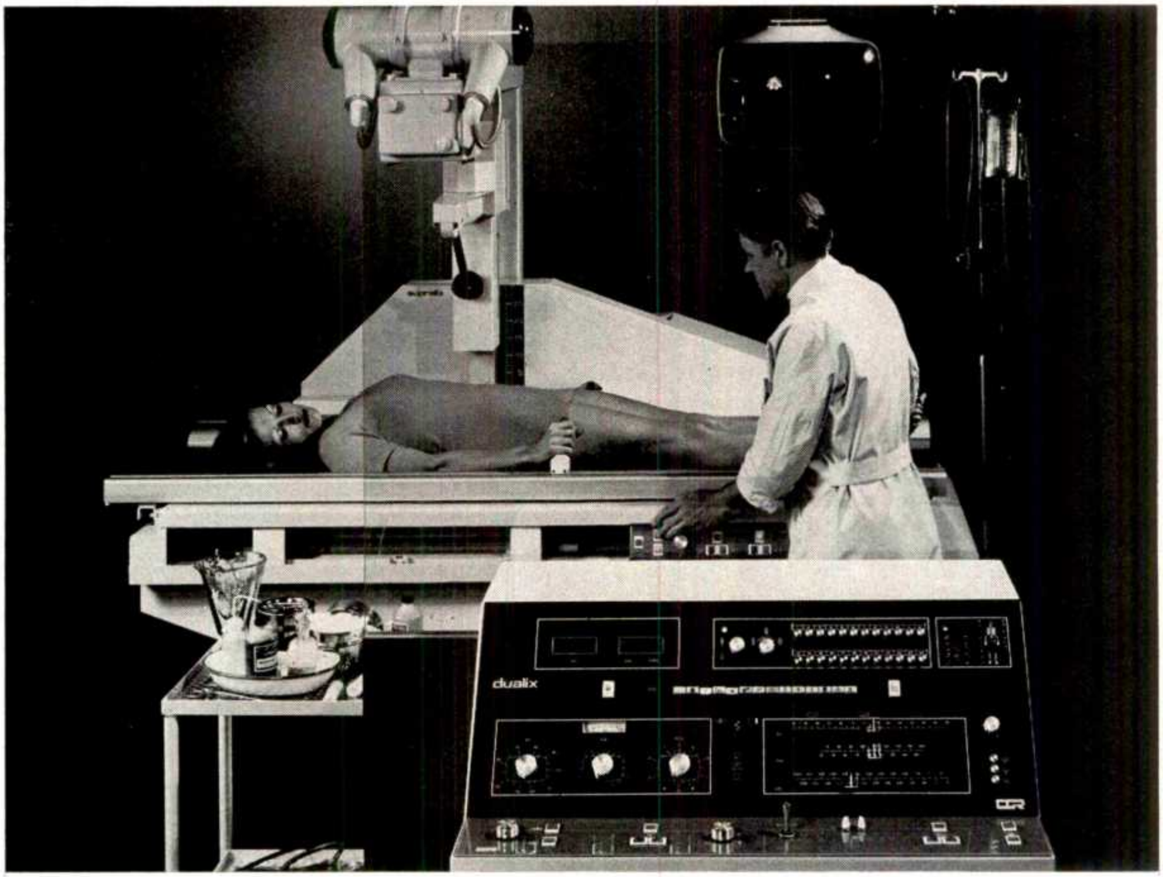

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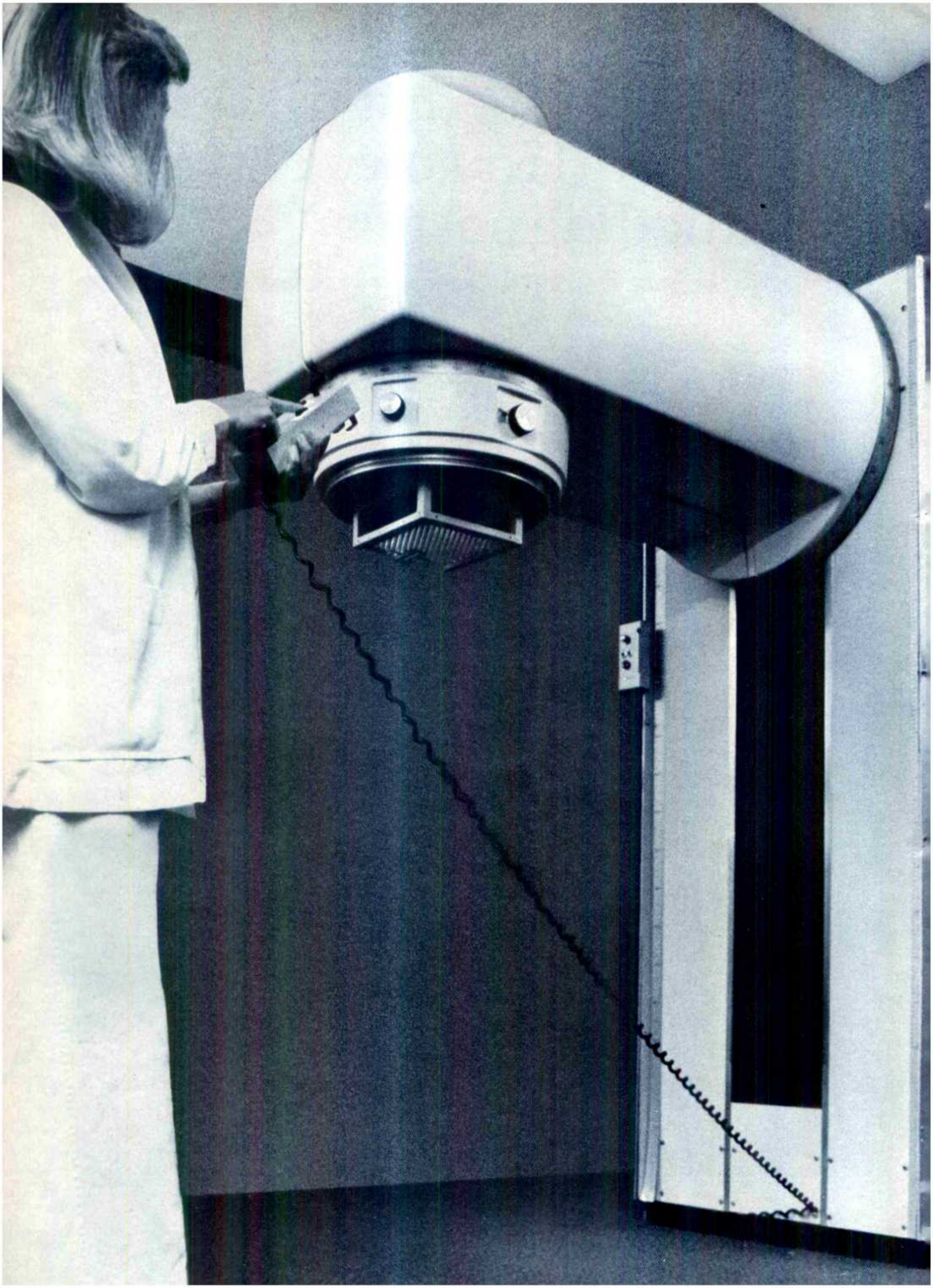

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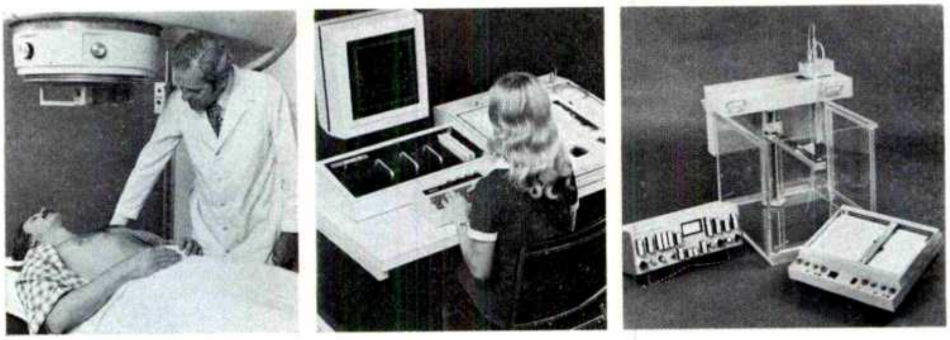

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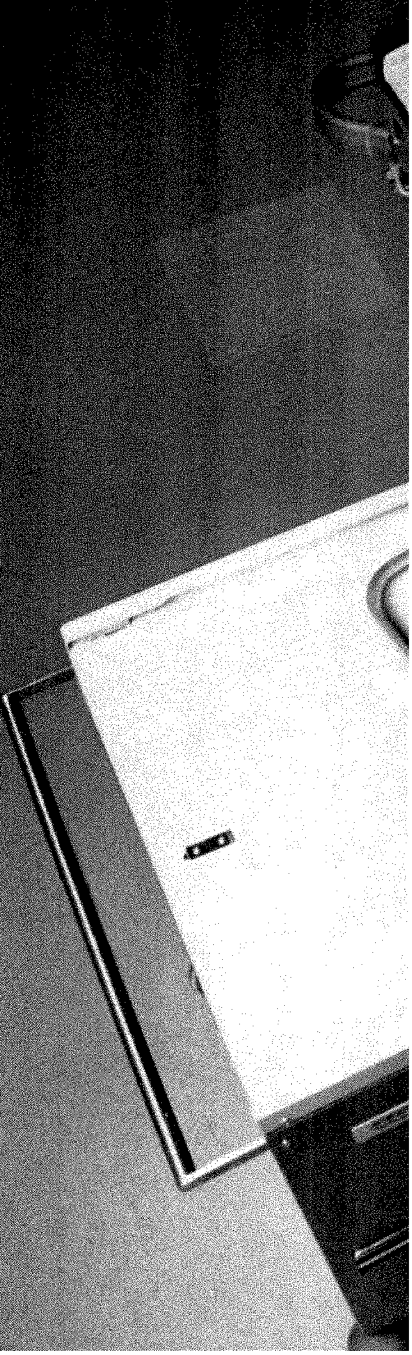

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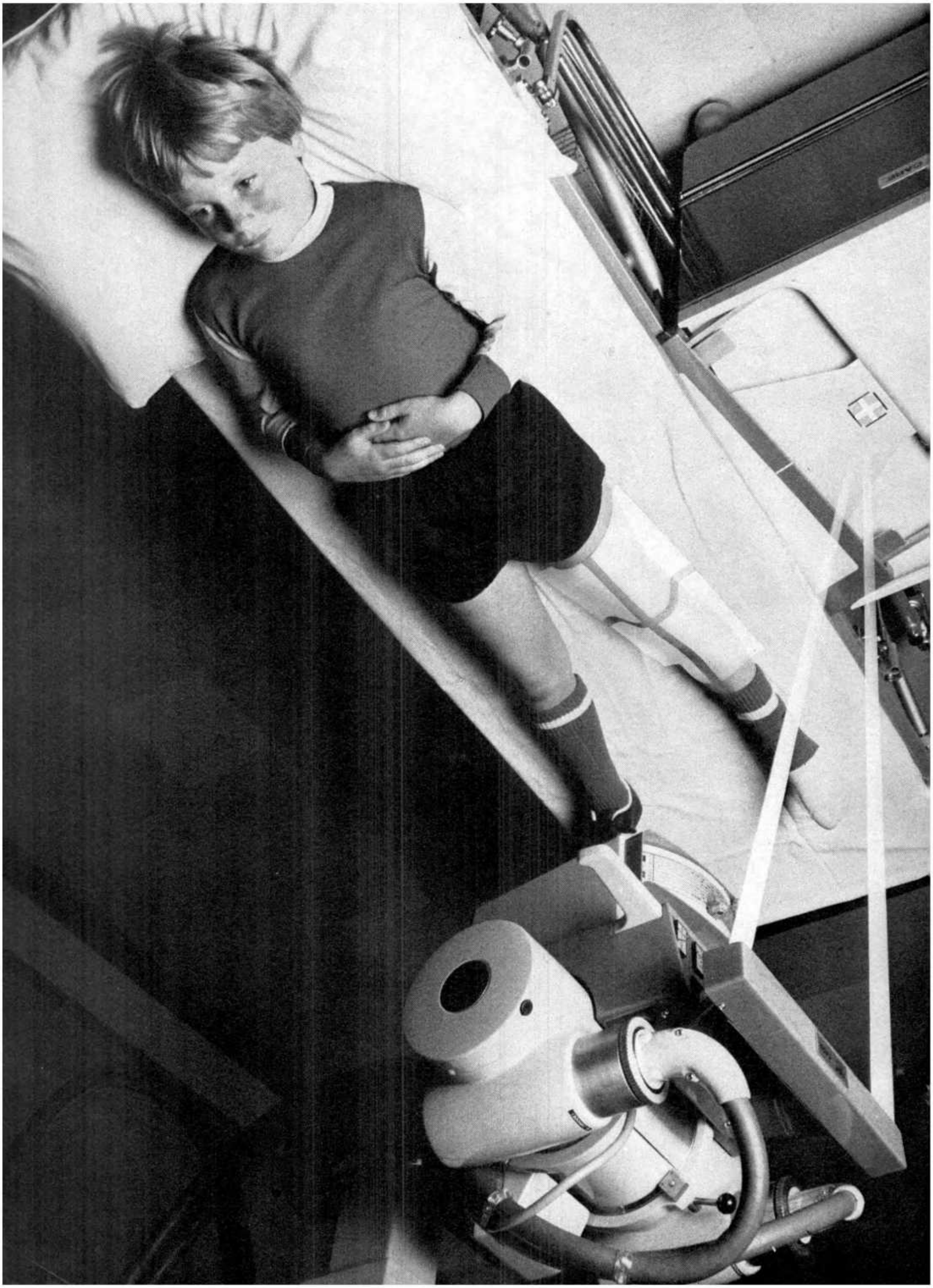

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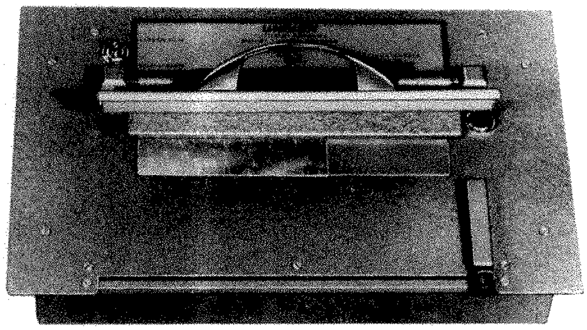

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The British Journal of Radiology

Radiology now

Screening for breast cancer*

In England and Wales 17,000 new cases of breast cancer in women are registered each year and the annual death toll amounts to 11,000 women (*Registrar-General Statistical Review, 1972*). There has been no reduction in the mortality from the disease for several generations; half the women die within five years of diagnosis and two-thirds within ten years (Brinkley and Haybittle, 1975). Despite this, breast cancer is a curable disease in that 20% to 30% of patients diagnosed as having early breast cancer will enjoy a normal lifespan without further obvious trouble, following treatment (Baum, 1976). The improved results seen in T1NO lesions (Cutler, 1968) *i.e.* a primary tumour less than 2 cm in size without nodal involvement, has stimulated interest in the possibility of detecting early breast cancers via mass screening programmes.

The initial results of mass screening for cancer of the breast, and indeed the whole concept and feasibility of such programmes were extensively reviewed at the Third International Symposium on the Detection and Prevention of Cancer held in New York in April 1976. Discussion centred around the cost and effectiveness of such programmes, the safety and accuracy of mammography, the possible role of thermography, the selection of women to be screened, and on the implications of providing, or attempting to provide, a comprehensive breast cancer screening programme. The controlled trial conducted by Strax *et al.* (1967, 1973) formed the basis for discussion. In this study, carried out by the Health Insurance Plan of Greater New York, 62,000 women aged between 40 and 64 were allocated randomly to a group offered annual screening for four years and a control group not offered any screening. The screening consisted of mammographic and clinical examination. After eight years the mortality from breast cancer was reduced by one third in the study group as compared with the control group. This benefit was confined to women over the age of 50. A significant contribution was made by mammography, and in 44 patients in whom the diagnosis of breast cancer was suspected on radiological evidence alone, 43 are alive and well after eight years.

This study has stimulated interest and inquiry into the implications of providing breast cancer screening services in the United Kingdom. The Department of Health and Social Security has established pilot study schemes at Edinburgh, Manchester and West London. The protocol for these centres includes the evaluation and comparison of clinical examination with mammography; investigating the safety of mammography and the acceptability of low radiation dose systems; assessing thermography in a screening context, and the performance of non-medical staff in examining breasts and reading mammograms. It was also hoped that the optimum interval between examinations could be determined, and an estimate made of the cost of such a service and its impact on the surgical workload.

Cancer detection rates in screening programmes vary from 0.5% to 1.4% (Pomerance *et al.*, 1976). In the West London study (Chamberlain *et al.*, 1975) 26 patients with breast cancer were discovered in the first 2,000 women examined. These patients, as in other surveys, fall roughly into three equal groups: in one third cancers were diagnosed on clinical examination alone, in one third discovered by mammography alone, and in the remaining third found by both procedures.

High referral rates and high biopsy rates have caused concern in screening clinics but these are lowered as experience is gained, and biopsy rates as low as 1.9% can be achieved (Pomerance *et al.*, 1976). In the West London experience more women are referred on clinical grounds than for mammographic abnormalities. The usual mammographic abnormality leading to biopsy in a clinically normal breast is the presence of microcalcification. Fine microcalcification is, however, seen in non-malignant breast abnormalities and is present in under half the carcinomas (Price and Nathan, 1975).

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*Reprint requests to: Dr. B. E. Nathan, Department of Radiodiagnosis, Hammersmith Hospital, DuCane Road, London W12 0HS.

Furthermore, this calcification may be at some distance from the carcinoma (Gibbs *et al.*, 1975).

Screening programmes present further problems to both surgeons and histopathologists. The surgeon may experience difficulty in localizing the lesion in a woman whose breasts may be clinically normal but whose mammogram might suggest a possible cancer. Specimen radiography is an invaluable aid in ensuring the suspicious area has in fact been removed, and in some centres specimen radiography is a routine procedure (Snyder and Rosen, 1971). There are also problems of diagnosis in borderline cases where histological difficulties arise in differentiating florid epithelial hyperplastic changes from non-invasive neoplastic cellular changes.

Considerable doubt has been cast on the safety of mammography, particularly if repeated examinations at intervals are envisaged. Traditional methods of breast radiography use slow non-screen film and a low kilovoltage X-ray beam with minimal filtration. Recent developments with vacuum-packed screen film techniques, however, have reduced radiation dosage considerably (Asbury and Barker, 1975; Price and Butler, 1970, 1975), and using the new rare-earth screen film combinations, skin doses are as low as 0.15 to 0.3 rad per exposure. This is well within the 2 rad limit per examination suggested by Ellis (1972), as suitable for screening programmes. Nevertheless, the subject remains controversial. Bailar (1976) using data from the New York study agrees that although mortality was reduced by one third in the study group, the evidence that mammography alone played a significant role was weak. He further felt that there was a lack of data on long-term effects of mammography and that the possible benefits of mammography had received more emphasis than its defects. As outlined, the radiation dosage at the present time is considerably less than the doses referred to in the New York study. It has also been argued that mass screening for breast cancer will never be practicable and that resources should be channelled elsewhere. Baum (1976) questions the traditional surgical approach to cancer of the breast. He suggests that the disease should be regarded as systemic until proved otherwise, and that it would be of greater value to expend time and energy improving the effectiveness of anti-cancer agents, than towards establishing nationwide screening programmes.

The logistics of setting up national breast screening services are formidable. Should the screening be offered to all women? How frequently should we re-examine the women? Should high risk groups be identified and seen at more regular intervals? These are questions the various pilot study schemes are attempting to answer. Although the New York experience suggests that women under the age of 50 do not benefit from screening, over half the cancers found in the West London study were in women under 50 years of age. The optimum time interval between examination is being studied, and early results suggest that re-examination every two years rather than annually may be a reasonable compromise. Screening only high risk groups (Thomas, 1975) would increase the yield but may be unacceptable to large numbers of women.

The cost of establishing a nationwide screening programme would be daunting. Not only would considerable funds be needed for the radiological equipment necessary, but the training of personnel to read mammograms, be they radiologist, radiographer or whoever, would present difficulties. Nevertheless, these difficulties could be overcome. Early experience in these clinics suggest that women appreciate and may eventually demand this service. We must hope that the early detection of the disease would in the long term reduce the need for prolonged, distressing and expensive hospital treatment, as well as saving many lives.

B. E. NATHAN.
J. L. PRICE.

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Book reviews

Radiotherapy in modern clinical practice. Edited by H. F. Hope Stone, pp. 358, illus., 1976. (Crosby, Lockwood Staples) £10.

This text-book of radiotherapy is said to be written not only for radiotherapists but also for those physicians and surgeons who collaborate with radiotherapists in the joint management of patients with malignant disease. To satisfy the interests of both is an almost impossible task and it is not surprising that this book does not entirely succeed.

The book starts with a technical chapter on the historical development of the modern radiotherapy department and concludes with a chapter on computing in radiotherapy. Between, are 11 chapters wirtten by consultant radiotherapists which highlight recent advances and attempt to define the place of modern radiotherapy, both radical and palliative, in the treatment of malignant tumours at various sites. Most of the chapters are well written and there is an extremely good chapter on neoplasms of the head and neck by Dr. Henk. It is a pity that the chapter on the reticuloses contains such unconventional views and the chapter on gynaecological neoplasms is limited to a description of the Cathetron and its uses.

The chapter on the radiobiology of clinical problems by Dr. Wiernik, though beautifully written, may be of less interest to a reader who is not a radiotherapist. It probably does not belong in this book.

This is an attractively produced volume, easy to read, well illustrated and contains valuable information set out in such a way that it can only help to encourage multidisciplinary co-operation.

THELMA BATES.

Panoramic Dental Radiography. By Lincoln R. Manson-Hing, pp. xi + 183, 183 illus., 1976 (Springfield, C. C. Thomas), $32.50.

This book is really for Dental Students and Clinicians rather than Radiologists and Radiographers. The opening two chapters describe the principles involved in making panoramic films of the jaws. There follows a useful comparative review of some 16 different types of apparatus—experimental and production commercial models. These pages well show how the value of the resulting radiograph varies considerably from one machine to another. The next three chapters outline some technical factors, artefacts and the anatomical features to be identified in pantomography.

The next three chapters, together forming about one-third of the text, review the general and special diagnostic uses of the technique and provide an atlas of a wide variety of abnormalities shown in pantomograms. Unfortunately the majority of the films shown were made with the Panorex type of apparatus which gives images less satisfactory than those obtained with some of the other types of equipment described earlier in the book.

The three concluding chapters review radiation hazards, film processing and viewing. There is a comprehensive bibliography.

Radiological readers are unlikely to find much here for them but nonetheless this is a comprehensive review of this radiographic technique to which they may helpfully refer at times.

DAVID H. TRAPNELL.

1976, *British Journal of Radiology*, *49*, 820–826

The pituitary fossa in Cushing's syndrome. A retrospective analysis of 93 patients

By D. P. MacErlean,* B.Sc., M.B., F.R.C.R. and F. H. Doyle, B.Sc., M.B., M.R.C.P., F.R.C.R.

Department of Diagnostic Radiology, Royal Postgraduate Medical School, Hammersmith Hospital, Ducane Road, London W.12

(*Received February, 1976*)

ABSTRACT

A retrospective analysis of the pituitary fossa in 93 patients with Cushing's syndrome is presented. Radiological evidence of a pituitary tumour was found in 20 of 86 patients with pituitary-dependent disease (23%). In 11 of the 20 patients, the diagnosis depended on analysis of lateral tomograms. None of the seven patients with disease which was not pituitary-dependent had evidence of an abnormal sella. One of 20 controls without known endocrine disease had an abnormal sella.

Naturally occurring Cushing's syndrome has three main causes. The first and most important in endocrinological practice is bilateral adrenocortical hyperplasia due to increased secretion of ACTH by the pituitary. This is sometimes referred to as Cushing's disease, following Harvey Cushing's original description of the clinical manifestations of basophil adenomas of the pituitary in 1932. The second is a tumour, either an adenoma or a carcinoma of the adrenal cortex. The third is the secretion of ACTH by benign or malignant tumours of non-endocrine origin, the ectopic ACTH syndrome. If patients with the ectopic ACTH syndrome due to an oat-cell bronchial carcinoma and patients on treatment with corticosteroids are excluded, the disease is pituitary-dependent in approximately 80% of cases (Hall *et al.*, 1974). The proportion of patients with pituitary-dependent Cushing's syndrome described as having radiological evidence of an intrasellar expanding lesions varies. In two series (Salassa *et al.*, 1959; Welbourn *et al.*, 1971), approximately 10% of patients had abnormal sellae. Other authors regard an abnormal sella as a rare event (Hall *et al.*, 1974; Sutton, 1975). The present study is an attempt at a critical evaluation of the sella in 93 patients with Cushing's syndrome. Assessment was made initially without knowledge of whether the disease was pituitary-dependent or not.

PATIENTS STUDIED

Sixty-six females and 27 males with clinical and biochemical evidence of Cushing's syndrome were studied. The ages ranged from 7 to 73 years with a mean of 37.6 years. A lateral radiograph of the skull, taken as part of the routine investigation of patients with Cushing's syndrome was available in each of the 93 patients. Lateral tomography of the sella, available in 60 patients, consisted of polytome hypocycloidal tomography at intervals of 3 mm in 50 patients and linear tomography at intervals of 5 mm in ten.

METHODS

Three separate analyses of radiographs were carried out. In the first, the assessment was made without knowledge of the cause of the syndrome. To the 93 plain lateral radiographs of the patients with Cushing's syndrome were added 20 lateral radiographs from patients referred from the casualty department for skull radiography because of minor trauma. In these 113 radiographs, three criteria of sellar abnormality, namely double contour of the floor and anterior wall, abnormal size and/or shape, and erosion or localized thinning of the lamina dura were separately analysed and scored as follows. A major abnormality was given a score of four and a minor or equivocal abnormality a score of one. A total score of four or more was considered to represent evidence of an abnormal sella.

In the second analysis, the lateral tomograms in the 60 patients in whom tomography had been carried out were analysed and scored in a similar manner. The tomographic equivalent of a pathological double contour was an excessive change in sellar contour on adjacent tomographic sections. Plain film and tomographic scores in the patients with pituitary-dependent disease were then compared.

In the third analysis, each fossa in the 93 patients was allocated to one of five categories, based on inspection of the plain films and tomograms when the latter were available (60 of the 93 patients). A Category 1 fossa was obviously abnormal on the plain lateral radiograph (Fig. 1). Category 2 consisted of fossae judged to have definite intrasellar tumours, but tomography was necessary in some instances to delineate or confirm the abnormality (Fig. 2). Category 3 comprised fossae about which there was a considerable element of doubt, even after inspection of both plain films and tomograms. These sellae were considered to raise the suspicion of a "possible" tumour (Fig. 3). In Category 4 the fossae were regarded as "probably normal" (Fig. 4), and in Category 5, the radiographs provided text-book examples of normal sellae (Fig. 5).

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Finally the lateral area of the sellae was measured on the tomograms as follows. The tomographic section on which the lateral sellar area was greatest was determined. A straight line was drawn from the highest point on the anterior wall of the sella to the highest point on the dorsum sellae. The radiograph was then projected with tenfold magnification on to a sheet of white cardboard. The outline of the sella was traced on the cardboard, cut-out and weighed. The area of the sella was determined by comparing the weight of the cardboard with the weight of a standard area. The measured area was then corrected for geometrical magnification.

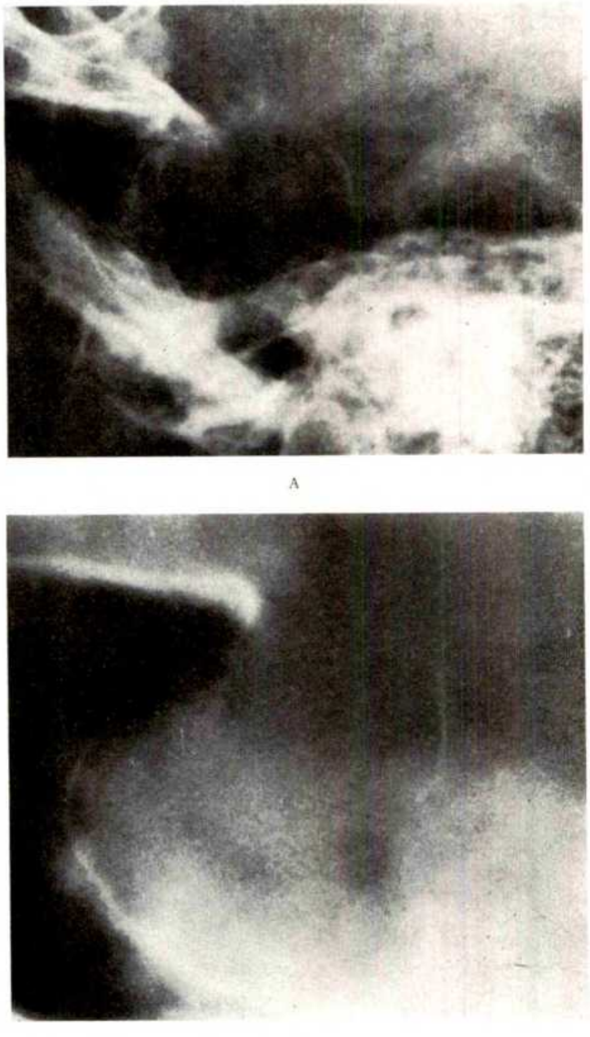


FIG. 1.

(A) Category 1 sella. Lateral radiograph showing obvious enlargement of the fossa with thinning and straightening of the dorsum.

(B) Lateral tomography not only confirms the diagnosis of a tumour but shows a large anterior and inferior extension into the sphenoid sinus not detectable on the plain film.

RESULTS

Of the 93 patients in this series, the syndrome was pituitary-dependent in 86. Four patients had an adrenal adenoma, one an adrenal carcinoma, one a bronchial carcinoid and one a malignant thymoma. The plain film scores of these 93 patients together with the 20 controls are shown in Table I. In the 86 patients with a pituitary-dependent syndrome, nine had a score of four or more, indicating an abnormal sella. Five had a total score of three and nine a score of two. The scores were one or zero in the remaining 63. All seven patients whose disease was not pituitary-dependent had scores of one or zero. The sella in one of the controls had a score of four, indicating an abnormal sella (Fig. 6). Three controls had a score of two, and 16 a score of one or zero.

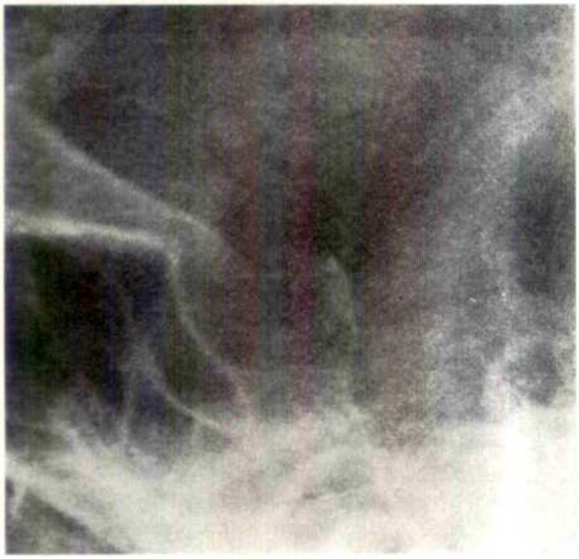
Fifty-seven of the 60 patients in whom lateral tomograms were available had pituitary-dependent disease. Five of these had a plain film score in excess of four. In the remaining 52 the score was less than four. Eleven patients with a plain film score of less than four had tomographic scores in excess of this (Fig. 7). Tomography had therefore added a further 11 patients to the nine who had already been allocated a patholgical score on the basis of the plain films only.

The categories of sella to which the total of 93 patients were allocated are shown in Table II.

TABLE I

PLAIN FILM SCORES IN 93 PATIENTS WITH CUSHING'S SYNDROME AND 20 CONTROLS

Score	Pituitary-dependent Number of patients	Not pituitary-dependent Number of patients	Controls Number of patients
4 or more	9	0	1
3	5	0	0
2	9	0	3
1	40	2	8
0	23	5	8
Totals	86	7	20



Seven patients with pituitary-dependent disease had obvious tumours on plain films, Category 1. Thirteen patients were allocated to Category 2, that is to say, had definite but not obvious tumours. Fifteen were in Category 3, that of a "possible tumour". Fifty-one of the sellae in the pituitary-dependent group were in Categories 4 or 5. All seven of the patients whose disease was not pituitary-dependent were allocated to Categories 4 or 5, these indicating probably normal or normal sellae.

Means and ranges of lateral sellar area are plotted against category of sella in Fig. 8. Mean sellar area increases progressively from Category 5 to Category 1. A wide overlap between the ranges is shown between adjacent categories. Only the sellae in Category 1 are clearly separated from those in Categories 3, 4 and 5. Sellae in Categories 3 and 4 overlap considerably with those in Category 2.

DISCUSSION

Harvey Cushing (1932) described the clinical manifestations of basophil adenomas of the pituitary

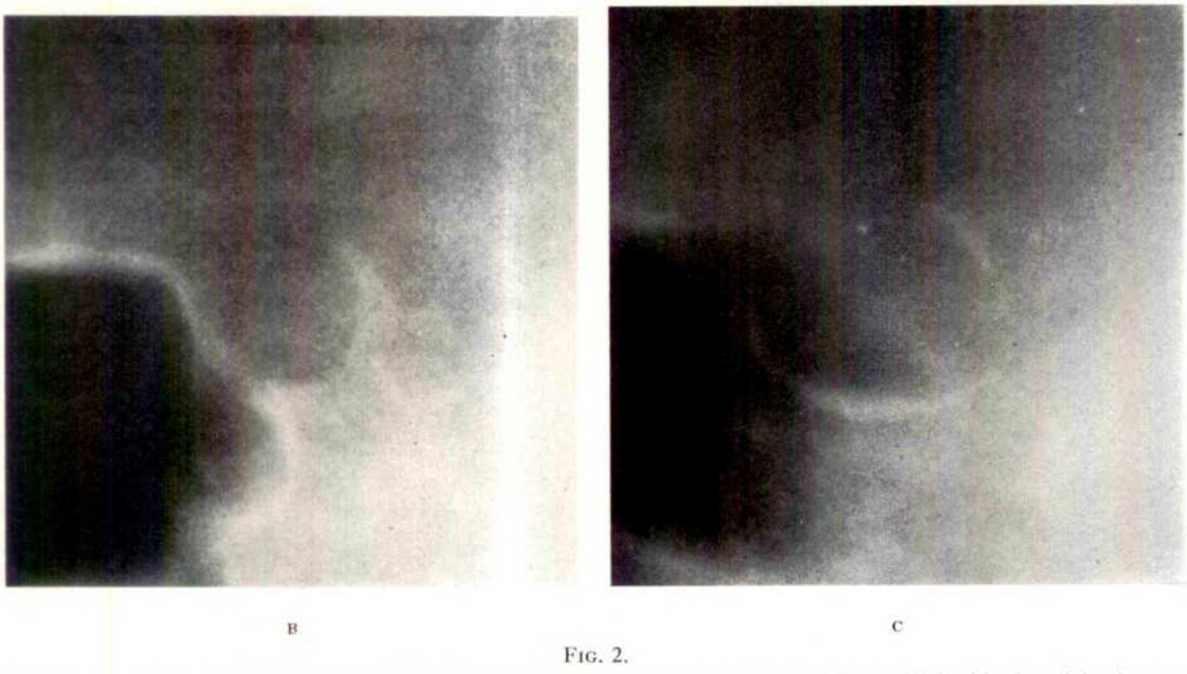


FIG. 2.

(A) Category 2 sella. This plain radiograph might easily be regarded as within normal limits. Slight thinning of the dorsum might be suspected. The eccentric anterior expansion into the sphenoid sinus is convincing only after analysis of the tomograms.

(B and C) Lateral tomographic cuts three mm apart. Localized expansion of the fossa and thinning of the dorsum are clearly shown in (C).

in 12 patients. Evidence from necropsy was available in eight. Small basophil adenomas were found in three and small adenomas of unspecified type in three others. The pituitary gland was reported to be normal in two. In a much larger post-mortem study of 97 patients, adenomas of the pituitary were found in 47, and in 31 of these the tumour was basophilic. (Plotz, 1952). A "deformed sella" was reported in only one patient. In these early studies, the striking feature is the high incidence of pituitary adenomas detected at post-mortem, and the very low incidence

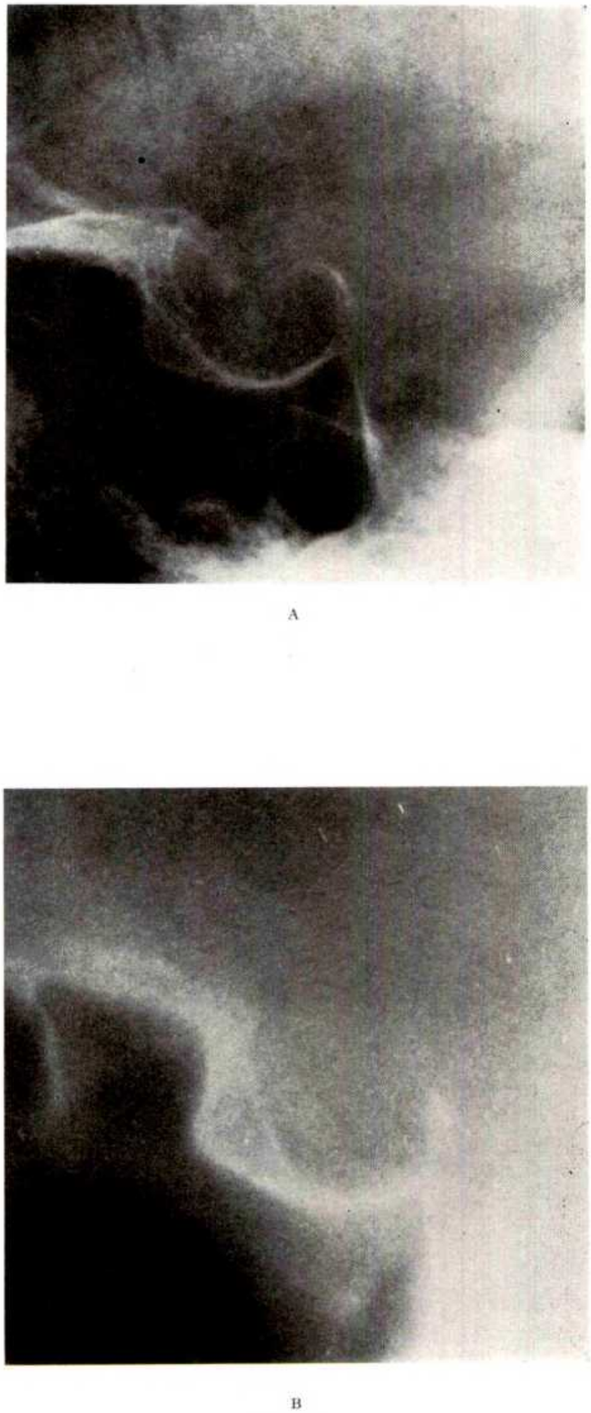


FIG. 3.

(A) Category 3 sella. The triple anterior contour with different thicknesses of lamina dura arouses suspicion that this may be a pathological fossa.

(B) Tomography tends to diminish the suspicion. The most anterior contour is angulated and not ballooned. The dorsum is somewhat straight.

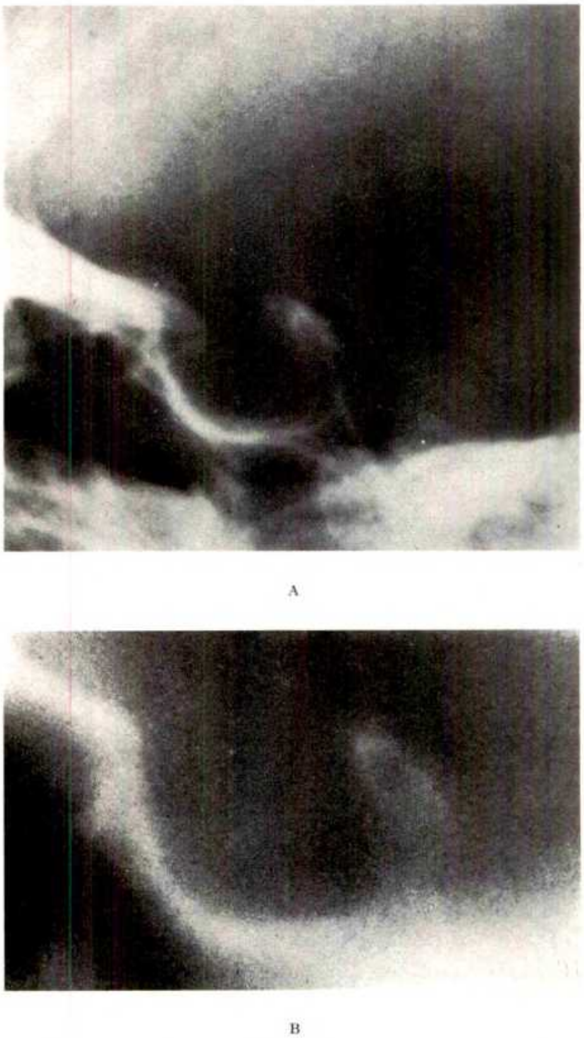


FIG. 4.

(A) Category 4 sella. The complex anterior bony contour of this fossa prevents allocation to a definely normal category.

(B) Tomography reassures the observer that the bony irregularity is within the sphenoid sinus and that this fossa is probably normal.

TABLE II

CATEGORIES OF SELLA IN 93 PATIENTS WITH CUSHING'S DISEASE

	Pituitary dependent			Not pituitary dependent		
Sellar category	Plain films only Number of patients	Plain films plus tomography Number of patients	Total Number of patients	Plain films only Number of patients	Plain films plus tomography Number of patients	Total Number of patients
1	3	4	7	0	0	0
2	1	12	13	0	0	0
3	1	14	15	0	0	0
4	14	25	39	0	1	1
5	10	2	12	4	2	6
Totals	29	57	86	4	3	7

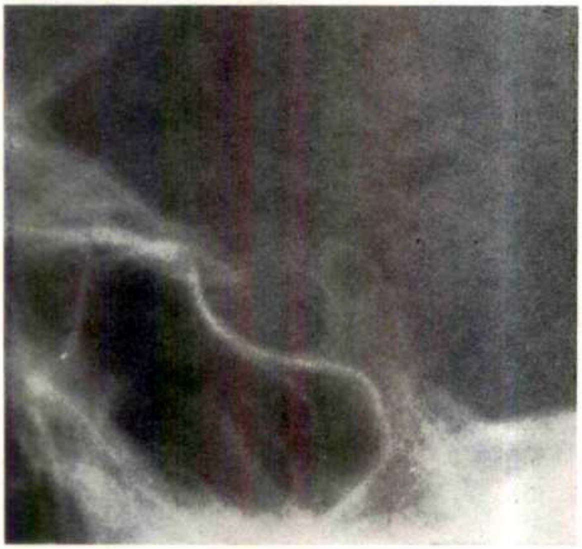


FIG. 5.

Category 5 sella. There is no hint of an abnormality in this sella.

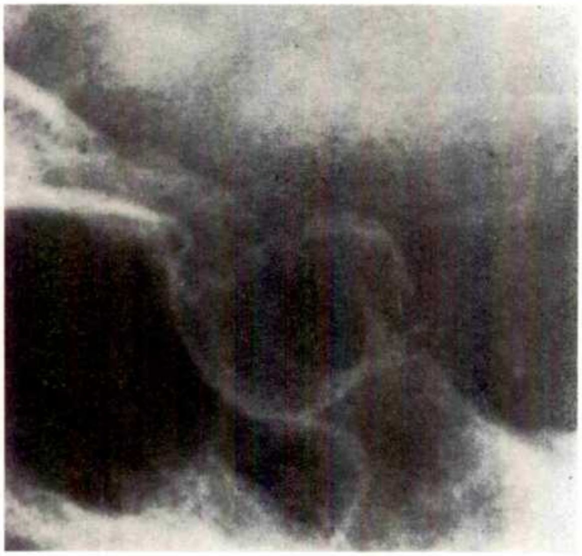


FIG. 6.

Lateral radiograph of control patient. This fossa was given a score of four and classified as abnormal. Unilateral bony bridging is present. It may be that this represents an anatomal variation, but definite exclusion of an intra-sellar expanding lesion is not possible.

of reported abnormalities of the pituitary fossa in life.

In two later series, radiologically demonstrable pituitary tumours were present in approximately 10% of patients before treatment (Salassa *et al.*, 1959; Welbourn *et al.*, 1971). In the present series of 86 patients with pituitary-dependent disease, an obvious tumour was present in seven (8%) and a definite tumour in 13 (15%). The finding of an abnormal sella in 23% of these patients depended to a large extent on careful assessment of high quality lateral tomograms. The diagnosis of an abnormal sella was determined by tomography in no fewer than eleven patients. Tomography was not performed in 29 of the pituitary-dependent group. These were all patients from the early part of the series, when lateral tomography was not routinely performed in patients with Cushing's syndrome. It is possible that the overall incidence of radiologically recognizable pituitary tumours would have

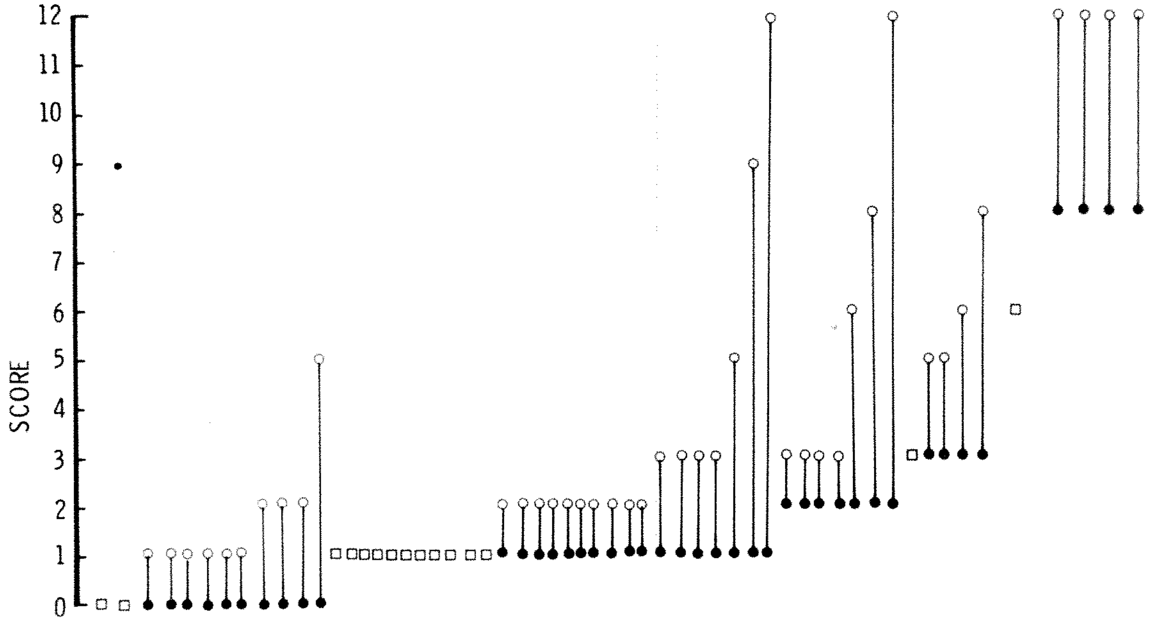


FIG. 7.

Comparison of plain film and tomographic scores in 57 patients with pituitary-dependent disease. Eleven patients whose plain film scores were within the normal range (less than four) were given a patholgoical score (four or more) on tomography. ● Plain film score. ○ Tomographic score. ☐ Score unchanged on tomography.

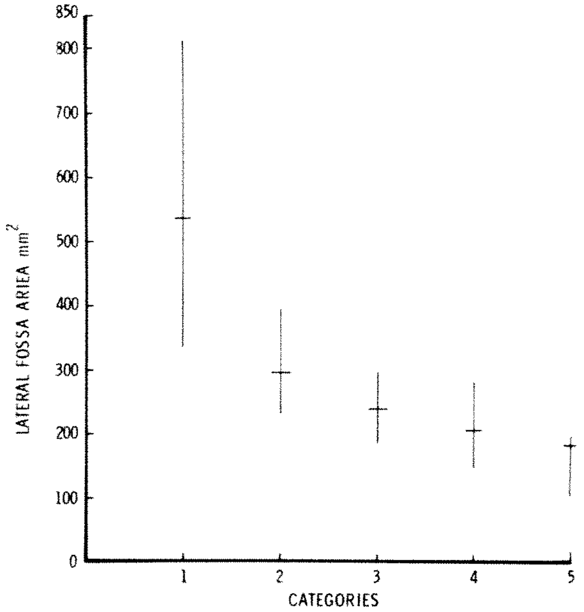


FIG. 8.

Means and ranges of maximum lateral area on tomography in the five categories of sella.

been higher than 23% had tomograms been available in these 29 patients.

The elaborate scoring procedure we adopted yielded no more information than the simple allocation of sellae into five categories. A total of 20 patients had pathological scores when the information from plain films and available tomograms was summated. The same 20 patients were allocated to Categories 1 or 2, and deemed to have obvious or definite tumours. The criterion of erosion or localized thinning of the lamina dura was not useful in these patients with Cushing's syndrome. Thinning and some unsharpness of the lamina dura in minor degree appeared to be relatively common. This may have reflected the generalized loss of bone which a proportion of patients with Cushing's syndrome manifest overtly by pathological fractures in their axial skeletons. A double or multiple contour of the floor and/or anterior wall is not uncommon in the normal sella. We were compelled to try to make the distinction between a pathological double contour and a double-contour which was due to minor anatomical or projectional variations. This was not an easy matter as it depended on a subjective appreciation of a level or degree of abnormality that was unquantifiable. The same applied to abnormalities of size and/or shape. Where the abnormality was gross, as in Fig. 1, there was no difficulty in allocating the sella to Category 1, that of an obvious tumour. The degree of abnormality of size and/or shape which determined the allocation to a pathological category proved impossible to define in a rigorous way.

Swanson and du Boulay (1975) have recently claimed that endocrinologists tend to accept minor variations of the pituitary fossa as evidence of an abnormality of the pituitary gland. They analysed in retrospect a group of 85 patients who had no overt clinical evidence of pituitary disease. Lateral radiographs of the skull and lateral tomograms of the sella were available as part of their neuroradiological investigation. Approximately 32% showed minor duplication of the floor or anterior wall and 17% showed thinning of the lamina dura on tomography. We have no reason to dispute these findings. The real problem is not to recognize minor variations in the sella but to decide when the degree of abnormality is sufficiently great to justify the diagnosis of an intra-sellar expanding lesion. The difficulties in doing this are reflected by the large number of fossae (15 out of the 86 patients with pituitary-dependent disease) which were placed in Category 3, a category which is neither definitely normal nor abnormal.

We have found that we cannot do better than to allocate a sella into one of five possible categories. This method of classification has been shown to have prognostic value in assessing the outcome of treatment of pituitary dependent Cushing's syndrome by pituitary implantation (Burke *et al.*, 1973). Fourteen of 57 patients were classified as having abnormal sellae (Categories 1 and 2). Only three were in remission at one year after implant and over half the patients were dead at five years. Ten patients had doubtful fossae (Category 3). Five out of ten were in complete remission at one year after implant and four remained so at five years. Of the remaining patients with normal sellae (Categories 4 and 5), 81% were in complete or partial remission at one year, and five years after implant the results were similar. The prognosis for patients with Category 3 sellae was therefore intermediate between that for patients in Categories 1 and 2 on the one hand, and in Categories 4 and 5 on the other.

Several authors have stated that objective measurements of the dimensions of a pituitary fossa are of little value in the diagnosis of pituitary tumours (Camp, 1949; Steinbach *et al.*, 1959; du Boulay and El Gammal, 1966; McLachlan *et al.*, 1970). The evidence of the present analysis supports this conclusion. Even the refinement of measuring the lateral area of the sella from the tomographic cut with the largest area failed to separate patients with definite tumours (Category 2) from those with probably normal fossae (Category 4). Although patients in Category 1 are clearly separated from those in Categories 3, 4 and 5, these are patients who by definition had obvious tumours by criteria which did not involve measurements of any kind.

This study has reinforced our conviction that high-quality lateral tomography is a necessary part of the radiological investigation of patients with proven abnormalities of pituitary function. We much prefer hypocycloidal to linear temography, believing that it increases the confidence with which sellae can be allocated to the five categories described above.

ACKNOWLEDGMENTS

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A quantitative study of the EMI values obtained for normal brain cerebral infarction and certain tumours

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ABSTRACT

A quantitative study has been made of the EMI numbers of normal brain, cerebral infarction and certain tumours. The scans were recorded on magnetic tape and analysed using a minicomputer linked to a graphic display unit. This system not only yielded 16 grey scales compared with the ten currently available, but was programmed to allow selected regions of the scans to be outlined. From these regions the computer calculated the area, the mean EMI number and its standard deviation.

It was found that in 15 normal brain scans, the EMI values obtained for normal frontal and temporal lobes were similar, but that the values for the basal ganglia and occipital lobes were significantly different from the first two regions and from each other. Ten cases of cerebral infarction and 30 cases of cerebral tumour were analysed, and it was shown that analysing representative areas was more informative than surveying the whole lesion. Whilst only half of the scans of brain tumours had a significantly altered EMI number compared with that of normal brain, enhancement of tumour density with sodium iothalamate revealed a consistent and significant elevation of the EMI number for all tumours. In particular, the value for enhanced meningiomas was almost double and malignant tumours more than a third larger than normal brain. It was not possible to differentiate quantitatively between astrocytomas and metastases.

The introduction of computerized transverse axial scanning (CTA) by Hounsfield in 1973 has resulted in a unique method of investigation of intracranial disorders. The practical details of the procedure (Ambrose, 1973) and the evaluation of the clinical applications (Gawler *et al.*, 1974; Paxton and Ambrose, 1974; Ambrose *et al.*, 1973; Ambrose *et al.*, 1976) have been described. The purpose of the present communication is to report the range of brain-tissue densities, expressed in EMI numbers, which are found in representative areas of the normal brain, and secondly, to show the quantitative results obtained for cerebral infarcts and various types of brain tumour before and after sodium iothalamate enhancement.

METHOD

Each CTA scan represents a slice of brain 8 mm or 13 mm thick which is displayed on a matrix of 160×160 elements, each element corresponding to an area of 1.5×1.5 mm. The "value" or EMI number in each element lies on an arbitrary scale between −500 and +500. The EMI numbers of various material are shown in Fig. 1.

McCullough *et al.* (1974) have related the EMI number (E) to linear attenuation coefficient (μ) according to the formula:

$$\mu = mE + c$$

where m and c are constants for operation at a given X-ray tube voltage. They found that at 120 kVp operation, the above formula provided agreement between the mean value of EMI numbers and μc for 73 keV photons to better than 0.5% in most cases.

In the present study, a 16 K Arcturus A18D minicomputer linked to a high-speed monochrome graphic display unit was used to analyse EMI scans stored on magnetic tape (Griver *et al.*, 1976). This system yielded 16 grey-scale levels compared with the ten currently available, and allowed selected regions of the scan to be outlined and the area, mean EMI number and standard deviation of EMI numbers within the area to be calculated.

In the first part of this investigation, the mean EMI values were determined for a standard area of 225 mm^2 for the frontal lobes, temporal lobes, occipital lobes and basal ganglia in 15 patients with normal EMI scans (Fig. 2). The second part was concerned with the EMI values obtained for ten patients with cerebral infarction of one week to three months duration due to vascular occlusion. In the

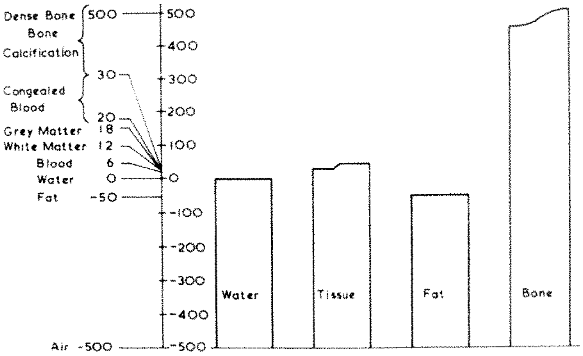

FIG. 1.

EMI absorption values of materials commonly encountered in clinical neuro-radiology.

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final section, 30 patients with intracranial tumours, including meningiomas, astrocytomas and metastases were investigated, before and after tissue density enhancement with sodium iothalamate. The method of administration and the qualitative results of such enhancement have been reported elsewhere (Ambrose *et al.*, 1975). In this section a comparison was made of the EMI numbers obtained for the whole tumour (excluding oedema and cysts) and of the selected area measuring 225 mm².

RESULTS

Estimation of normal EMI scan values

The mean EMI scan values in the frontal lobes, temporal lobes, occipital lobes and basal ganglia were determined from an area of 225 mm² in 15 patients who were considered to have normal EMI scans (Table I). The range of normality was taken as ±2 standard deviations, *i.e.* the probability (p) of a normal region being outside the range of normality, assuming a gaussian distribution is 0.0454, or approximately 1 in 20.

A comparison of each area with its counterpart in the opposite hemisphere using paired students-t tests, showed no significant difference. There were no significant differences (again using paired students-t tests) between the frontal and temporal lobes, but the EMI values for the basal ganglia and occipital lobes were significantly different from the other two regions and from each other.

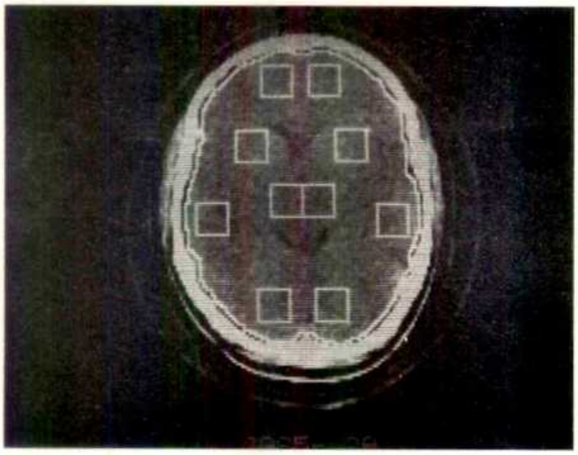


FIG. 2.

Location of standard areas in the brain scan, each of 225 mm².

TABLE I

EMI NUMBERS FOR DIFFERENT REGIONS OF THE BRAIN

Area	EMI numbers	Standard deviation	Range of normality $P=0.0454$
Frontal lobes	17.5	1.2	15.1–19.9
Temporal lobes	17.6	1.3	15.0–20.2
Occipital lobes	18.9	2.0	14.9–22.9
Basal ganglia	16.6	1.0	14.6–18.6

In addition, the mean value of the total area within the skull was found in all 15 patients. The mean value obtained was 17.6 with a standard deviation of 1.0. However, these figures are not particularly useful as they give no information concerning the range of values encountered within the different regions of the brain and ventricular system.

Estimation of EMI scan values for cerebral infarction

Ten patients with cerebral infarction due to vascular occlusion were investigated. In the first instance, the total area of infarction was examined and the EMI number and standard deviation determined.

In each case the difference between the EMI number of the infarcted area and the normal for the region under examination was calculated. The mean and the standard deviation of this difference for the ten patients was found to be -5.0 ± 2.7 for the entire area of infarction and -6.3 ± 3.0 for selected areas.

In delineating the entire area of infarction, inevitably some adjacent areas of brain were included as well as areas where the ischaemia was less pronounced. These factors would account for the lesser difference from the normal brain compared with a selected, circumscribed area. However, while selecting a representative area resulted in a greater mean difference of EMI values from the normal, both methods afforded a consistent reduction of EMI values. No systematic attempt was made to correlate the duration of the infarction with the EMI numbers.

Estimation of EMI scan values for tumour, before and after contrast enhancement

Thirty patients were investigated, ten patients for each tumour group consisting of meningiomas,

TABLE II

EMI VALUES FOR THE WHOLE AND SELECTED AREAS OF INFARCTION

Average area mm²	Mean EMI number	Standard deviation
1285	12.4	2.8
225	11.2	3.0

astrocytomas and metastases. In each patient, the EMI number was obtained firstly for the total area of the tumour excluding the surrounding oedema and any tumour cyst. Secondly, a standard representative area (Fig. 3) of 225 mm² was measured for each tumour. The mean EMI number and standard deviation for the ten patients in each group were calculated and are shown in Tables IIIA and IIIB.

It is clear from these results that the quantitative differences betwen a metastasis and an astrocytoma are indistinguishable. Moreover, whilst a lesion may be suggested on the unenhanced scans, only 4/10 meningiomas, 2/10 astrocytomas, and 4/10 of the metastases were found to be out of the normal range ($P=0.0454$). Following enhancement with sodium iothalamate (Table IIIB), all patients were found to have an EMI number outside the normal range, the difference in the EMI values being even more marked when only a selected area of the tumour was examined. There was no significant alteration in the size of the tumour area following enhancement, but the demarcation between tumour and surrounding oedema became more pronounced.

The increase in EMI values of the meningiomas was particularly noticeable following enhancement. However, the alteration in patients with astrocytomas and metastases was such that whilst unequivocally confirming the presence of a tumour, it did not permit distinction between the two lesions.

TABLE IIIA
EMI VALUES FOR UNENHANCED TUMOUR AREAS

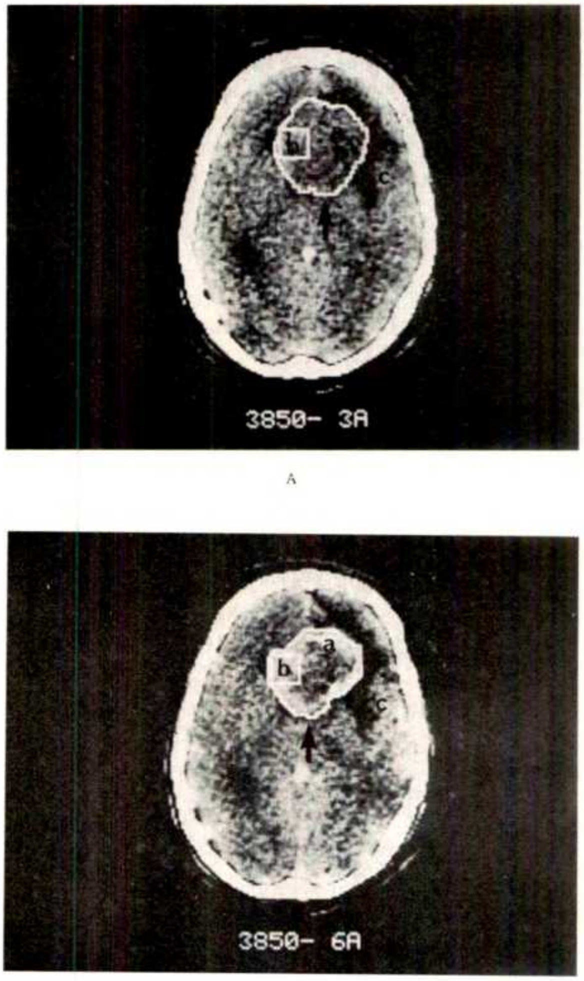
Turnover type	Average area mm²	Mean EMI number	Standard deviation
Meningioma	2250 225	22.1 21.3	±2.9 ±3.1
Astrocytoma	1886 225	15.7 17.9	±1.3 ±2.6
Metastasis	880 225	16.8 17.8	±3.2 ±2.5

TABLE IIIB
EMI VALUES FOR ENHANCED TUMOUR AREAS

Tumour type	Average area mm²	Mean EMI number	Standard deviation
Meningioma	2224 225	36.8 36.4	±4.7 ±5.1
Astrocytoma	1863 225	20.3 24.1	±2.4 ±2.6
Metastasis	800 225	22.5 24.4	±4.2 ±2.8

DISCUSSION

In an unpublished study, using a specially constructed phantom, it was found that under certain conditions (*e.g.* bone-tissue interface), the scanner was unable to contend with large density changes, resulting in "overspill" from the high to low density areas. The magnitude of the overspill was directly related to bone thickness and decreased with increasing the tube voltage. With 100 kV operation and large skull thickness (11 mm), this overspill could effect adjacent brain tissue for 1.5–2.0 cm,



A

B

FIG. 3.

Malignant astrocytoma of the genu of the corpus callosum, (A) before sodium iothalamate enhancement and (B) after enhancement. Tumour outline indicated by an arrow, a = tumour, b = standard representative area and c = oedema.

resulting in the EMI values being 5 to 20 more than expected, and could account for the higher numbers obtained for the occipital lobes and also the larger standard deviation.

It was frequently difficult to demarcate precisely the margins of the abnormal area being investigated. In practice it was found that while there was a less than 10% margin of error on repeated delineation of the same area, selecting a standard area representative of the whole lesion provided the most consistent results. A further problem arose in subsequent examinations, of reproducing the initial level of scan section. Normally, the repeated sections were within 5 mm of the original cut and except for very small lesions, this difference had little significant effect of the total area demarcated and none at all on the EMI values obtained for the standard areas. Finally, there are random variations for the values obtained by the EMI-Scanner, inherent in the machine and possibly depending upon the length of time it had been working and the ambient temperature. This variation does not exceed one EMI number.

Initially, when obtaining values for normal brain, values were derived for the total area within the skull; however, when different regions of the brain were compared, it was evident that significant differences between the values obtained for these areas existed. Moreover, when considering possible areas of abnormality, particularly of the basal ganglia, comparison with the EMI values for the appropriate region of normal brain facilitated the recognition of significant differences.

It was found that areas of cerebral infarction consistently showed a reduction of three to six EMI numbers below the appropriate normal value and the greater accuracy of calculating the values of a selected area rather than the whole lesion became apparent. Little attempt was made to relate the duration of the infarction with EMI values, but a correlation of the EMI number with the evolution of the infarct almost certainly exists.

In considering the EMI values of the tumours, nearly half of the meningiomas had an initial EMI number at least three above the normal. All these tumours showed a very large increase of the EMI number following enhancement, which characteristically was 16 to 20 EMI units above the value of normal brain tissue.

Less than one-third of the unenhanced scans of metastases and astrocytomas showed a significant difference of the EMI number from the normal. In the remainder of these malignant tumours, although the presence of a tumour was clearly indicated by the concomitant oedema and distortion of the ventricular system, it is important to note that without enhancement, the EMI number was not distinguishable from that for normal brain. The reason for this is that the concept of the range of normality refers to variation between normal patients. Paired tests between normal and proven abnormal tissues within scans would probably yield more sensitive measures for suspected abnormality, but these tests are not always feasible, particularly for the basal ganglia and occipital lobes. However, with enhancement, there was an increase in the mean EMI number by three or four for whole tumour values improving to more than seven when only a selected area of tumour was considered.

In conclusion, this study has established the EMI numbers for normal and infarcted brain tissue and certain types of tumour. The results confirm in a quantitative manner, the benefits of enhancing tumour density with sodium iothalamate. Secondly, they suggest that a more accurate conclusion concerning abnormal brain tissue can be achieved by examining selected, representative areas rather than the whole lesion. Finally, the sensitivity and reproducibility of the method should make it possible to follow the progress of tumours and their response to treatment. This aspect is currently under investigation.

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Estimation of glomerular size and number from radiographs of the kidney

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ABSTRACT

In 32 adult human kidneys obtained at necropsy, renal dimensions, measured from radiographs, were correlated with the number and cross-sectional area of glomeruli, determined by point-counting and computerized image analysis. Cortical area, measured from post-mortem angiograms, was poorly correlated with glomerular area and was not significantly correlated with glomerular number per kidney. The area of the whole kidney was poorly correlated with the number of glomeruli per kidney and was not significantly correlated with glomerular area. However renal dimensions, particularly total renal area, were highly significantly correlated with the product of glomerular area and number. This may allow glomerular numbers to be estimated in life but will not assess loss of glomerular surface area due to hyalinization of glomeruli or change in their shape with age. As cortical dimensions declined in the ageing kidney, the number of glomeruli per unit volume increased.

The dimensions of the human kidney, measured from radiographs, are well correlated with its post-mortem weight (Moell, 1961; Ludin, 1967; Griffiths *et al.*, 1976). The reduction in renal size (Roessle and Roulet, 1932; Dunnill and Halley, 1973) and function (Lewis and Alving, 1938; Davies and Shock, 1950) which occurs with ageing is accompanied by a loss of cortex and of glomerular surface area and numbers (Moore, 1931; Darmady *et al.*, 1973; Dunnill and Halley, 1973; McLachlan *et al.*, 1976). Although a relationship has been claimed between renal size, assessed radiographically, and function in healthy and diseased adult kidneys (Ladefoged and Pedersen, 1968; Andersen and Morgensen, 1973), no relationship has been established between renal size and the number and dimensions of glomeruli.

Methods which can be employed to determine glomerular characteristics have recently been developed and refined. In kidneys obtained at necropsy we have examined the extent to which renal measurements made from radiographs provide indices of glomerular numbers and dimensions. Glomerular numbers were estimated by stereological methods (Dunnill, 1968; Weibel, 1969; Underwood, 1970; Elias *et al.*, 1971) which allow conclusions about structure in three dimensions based on interpretation of two-dimensional microscopic images. Glomerular dimensions were measured by computerized image analysis.

MATERIALS AND METHODS

Thirty-two kidneys were obtained at routine necropsy from 32 subjects aged 20–91 years (mean 64 years). Nineteen were male, 13 female. Macroscopic examination of the kidneys, including post-mortem pyelography (Griffiths *et al.*, 1976), showed no evidence of scarring, cysts or calyceal deformity. Mild hypertensive vascular disease was evident histologically in seven kidneys; 14 others showed arteriosclerosis. Three additional kidneys, two diseased, the other from a young girl (Table I), were also studied but were excluded from the statistical analyses. All kidneys were examined within a few hours of necropsy.

Perirenal fat was removed leaving the renal capsule intact. Renal volume, including hilar structures, was measured by Archimedes' principle. Pyelography and angiography were performed as previously described (Griffiths *et al.*, 1976). Fine grain film (Kodak Industrex M) was used for angiography and developed by hand. Radiographs were obtained at a focus-film distance of 180 cm with the kidneys resting on the film envelope. Measurements from these were not adjusted for magnification. Total renal area and "cortical" area, defined as the area peripheral to arcuate arteries, were measured from antero-posterior angiograms. Cortical volume was estimated from these angiograms by the method of Hegedus and Faarup (1972) and expressed as a fraction of renal volume similarly estimated. "Area of renal substance", measured from antero-posterior pyelograms, was defined as the difference between the areas of the whole kidney and the collecting system. Measurements were made by computerized image analysis. Tracings from radiographs were presented to the Quantimet 720 D (Image Analysing Computers Ltd.). This apparatus, which allows rapid accurate measurement of dimensions, uses a 720-line plumbicon camera to scan images, data being analysed by linked computer modules. Glomerular dimensions (see below) were measured by similar methods.

TABLE I

DETAILS OF SUBJECTS NOT INCLUDED IN STATISTICAL ANALYSES

Age (years) and sex	Renal disease	Renal area (cm^2)	Mean glomerular tuft area ($\text{mm}^2 \times 10^{-2}$)	Glomeruli per kidney	
				Observed	Predicted (see text)
17, female	None	38.5	0.67	1466980	1813710
55, male	Diabetic nephropathy	60.7	1.47	1063600 (23% hyalinized)	1350120
77, female	Rheumatoid disease and hypertension	29.4	1.36	434340 (38% hyalinized)	661900

Glomerular numbers were calculated by stereological methods (Dunnill 1968; Weibel, 1969; Underwood, 1970; Elias *et al.*, 1971) which are more fully described elsewhere (McLachlan *et al.*, 1976). Point-counting of glomeruli, which for this purpose were considered to be the structures bounded by Bowman's capsule, was performed by superimposing an 80-point grid on photographs of randomly selected histological sections, stained by haematoxylin and eosin. Totally hyalinized glomeruli (Papper and Vaamonde, 1971; Kaplan *et al.*, 1975) which formed on average, 1.3 (SD 1.8) % of the total number in each kidney were included in the counts. Since significant inter-observer error occurs in point-counting (McLachlan *et al.*, 1976) all counts were made by one observer. Calculations of glomerular number per kidney were based on the volume of fresh kidney minus the volume of the hilar tissue, which was cut off after the radiological procedures. This gave a mean renal volume of 132.5 (SD 31.5) cm^3. (Mean increase in volume after barium injection and fixation was 9.2%). The cross-sectional areas of the tuft and capsule of 100 glomeruli were measured in each kidney by computerized image analysis by the Quantimet 720 D. Tracings obtained from photographs of histological sections were used (McLachlan *et al.*, 1976). Measurements were adjusted for photographic magnification but not for changes due to tissue processing. For each kidney mean tuft and capsule areas, the means of these 100 measurements, were derived.

RESULTS

No significant differences existed between the seven kidneys showing mild hypertensive vascular disease and the other 25. Renal area and volume were significantly correlated ($r=0.69$, $p<0.001$). Both were significantly smaller in females ($p<0.01$); glomerular number and area were not. Cortical volume was calculated to be 55 (SD 5.9) % of renal volume. For the 32 kidneys, mean figures for mean glomerular tuft and capsule areas were, respectively, 1.44 (SD 0.42; range 0.94 to 2.40) and 2.14 (SD 0.55; range 1.51 to 3.35) $\text{mm}^2 \times 10^{-2}$. The number of glomeruli per kidney was, on average, 1309280 (SD 359960; range 594531 to 2000310), the number per cm^3 was 10140 (SD 2850; range 5340 to 15720). A significant correlation ($r=0.43$, $p<0.05$) existed between renal area and glomerular number per kidney but not between renal and glomerular areas. Cortical area was significantly correlated with mean glomerular tuft area ($r=0.43$, $p<0.05$) and capsule area ($r=0.40$, $p<0.05$). No significant correlation existed between cortical area and glomerular number per kidney. The product of mean tuft area and glomerular number per kidney was highly significantly correlated with cortical area ($r=0.61$; $p<0.001$) and with renal area ($r=0.67$; $p<0.001$) (Fig. 1). Correlation between this product and area of renal substance was poorer ($r=0.54$; $p<0.01$). A significant negative correlation ($r=-0.41$; $p<0.05$) existed between cortical area and glomerular number per cm^3. The significance of correlations was not changed by subtraction of the number of hyalinized glomeruli. Results in the three additional kidneys are shown in Table I. The number of glomeruli in these kidneys was predicted using the regression equation quoted in Fig. 1 from a knowledge of renal and mean tuft areas. Predicted figures are in reasonable agreement with those observed.

DISCUSSION

Attempts to relate renal size and function in children (Berg *et al.*, 1970) and in adults (Ladefoged and Pedersen, 1968; Andersen and Morgensen, 1973) assume a relationship between renal dimensions and functional glomerular mass. Several studies (Moell, 1961; Ludin, 1967; Griffiths *et al.*, 1975), including the present one, have established that the dimensions of the kidney, measured from

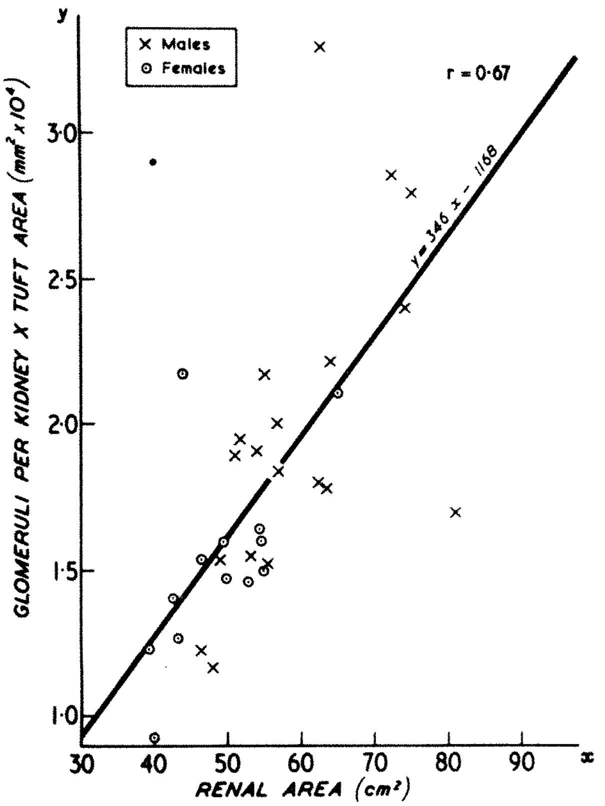

FIG. 1.

Renal area is highly significantly correlated with the product of glomerular number and mean tuft area ($p < 0.001$). The regression equation $y = 346x - 1168$ was used to predict glomerular numbers in three other kidneys (see text and Table I). The product of glomerular number and area is slightly smaller in females ($p < 0.05$); renal area is also smaller ($p < 0.01$).

radiographs, are highly significantly correlated with its post-mortem weight and volume. However the proportion of the normal kidney formed by each of its constituent parts varies. Occasionally, 17 per cent of its post-mortem weight may be due to fat in the renal sinus (Griffiths *et al.*, 1975). Dunnill and Halley (1973) recorded a four-fold variation in the fraction of cortical volume taken up by tissue other than glomeruli and tubules. About one-third of the number of glomeruli in the kidneys from apparently normal children (Emery and Macdonald, 1960) and adults (Kaplan *et al.*, 1975) may be sclerosed and presumably non-functioning. Cortical volume, expressed as a fraction of renal volume, also varies (Hegedus and Faarup, 1972; Dunnill and Halley, 1973).

This variation in cortical fraction does not appear to be due to post mortem change or mode of death. Hegedus and Faarup (1972), who calculated cortical volume from angiograms performed in healthy adults *in vivo*, concluded that, on average, it comprised 54 (SD 4.2) % of renal volume. Applying their methods to the post-mortem angiograms performed in the present study, in subjects dying from various conditions, we obtained a figure of 55 (SD 5.9) %. Dunnill and Halley (1973) used point-counting techniques in sliced kidneys removed after death due to trauma. Their results in adults are similar (mean 61, SD 5.4, %). These observations suggest that post-mortem shrinkage of the kidney, the importance of which was emphasized by both of these groups of investigators, affects cortex and medulla to a similar degree.

Our figures for glomerular numbers and dimensions are in reasonable agreement with those quoted by others from smaller series (Arataki, 1926; Vimtrup, 1928; Moore, 1931; Elias and Hennig, 1967; Dunnill and Halley, 1973), despite differences in technique. Computerized image analysis, a method applied only recently to biological tissues, enabled us to measure in each kidney large numbers of glomerular sections which, as Elias and Hennig (1967) have indicated, are necessary for determination of glomerular dimensions. We have not attempted to correct these figures for post-mortem changes or the effects of tissue processing. According to Elias and Hennig (1967), dehydration and embedding of the material for histology would offset the increase in volume due to fixation and injection of barium.

We established no significant correlation between cortical area and the number of glomeruli per kidney, though both decline as the kidney ages (Moore, 1931; Dunnill and Halley, 1973; Griffiths *et al.*, 1976; McLachlan *et al.*, 1976). With this diminution in cortical dimensions, glomeruli become more densely distributed. Though in the adult glomeruli occupy less than ten per cent of cortical volume, tubules forming about 65 – 85 % (Dunnill and Halley, 1973), the dimensions of glomeruli and proximal tubules are positively correlated (Oliver and MacDowell, 1961; Darmady *et al.*, 1973). Cortical thickness to some extent reflects these dimensions; we demonstrated that cortical area is correlated with glomerular area. In statistical terms the relationship is far from close, being significant only at the 5% level, probably due to the wide variation in the volume of cortical interstitial tissue noted by Dunnill and Halley (1973).

Our method of calculating glomerular numbers is based on measurements of renal volume. Despite the fact that renal area and volume are themselves highly significantly correlated, correlation between renal area and glomerular number is poor. There was no significant correlation between renal and mean glomerular areas. Glomerular number and mean tuft area both varied widely; a negative correlation exists between these two variables (McLachlan *et al.*, 1976). Their product, which we take to be an index of total glomerular mass, is highly significantly correlated with the areas of both cortex and the whole kidney. It is less significantly correlated with the area remaining after subtraction of the part occupied by the collecting system. As a result, it may be possible to estimate this product of glomerular number and area from radiographs obtainable *in vivo*. If tuft area is known, possibly by microdissection (Oliver and MacDowell, 1961; Darmady *et al.*, 1973) of biopsy material, the number of glomeruli within a kidney may be predictable. Using the regression equation quoted in Fig. 1 we calculated glomerular numbers in three kidneys which were not included in the statistical analyses. One was a growing kidney, with small glomeruli; two were diseased. Though numbers were overestimated, results suggest that prediction of glomerular numbers is feasible.

However, these calculations do not estimate functional glomerular mass. In the two diseased kidneys 23 and 38% of glomeruli included in the estimates were completely hyalinized. These obviously non-functioning glomeruli formed, on average, 1.3% of the toal number in the other kidneys studied. This fraction, which tends to increase with age (Kaplan *et al.*, 1975; McLachlan *et al.*, 1976) may be much higher. It ranged from none to one-third of all glomeruli in the kidneys of 122 normotensive subjects studied at necropsy by Kaplan *et al.*, (1975). Though correlations between glomerular numbers and renal dimensions were not changed when we excluded totally hyalinized glomeruli, a range as wide as that quoted by these authors would make accurate prediction of the number of functioning glomeruli very difficult. Furthermore, the deep indentations which are present in the tufts in early adult life tend to disappear in the elderly resulting in a reduction in surface area which is not reflected in cross-sectional area (McLachlan *et al.*, 1976). This, coupled with loss of glomeruli, must contribute to the decline in renal function which occurs with aging (Lewis and Alving, 1938; Davies and Shock, 1950). Our evidence suggests that neither hyalinization nor this change in shape will be indicated by measurement of the renal dimensions obtainable from radiographs. At best these measurements can provide only imperfect indices of glomerular surface area in the ageing kidney.

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Book review

Engineering compendium on radiation shielding. Vol. II: *Shielding Materials.* Edited by R. G. Jaeger, E. P. Blizard, A. B. Chilton, M. Grotenhuis, A. Hönig, T. A. Jaeger and H.H. Eisenlohr, pp. x + 436, 1975 (Berlin, Springer-Verlag), $131.20.

This volume, to which 22 specialists from eight countries have contributed, completes the three-volume compendium sponsored by the International Atomic Energy Agency.

The first half of the book is concerned with materials which are used for gamma radiation shielding. As well as information on atomic properties, such as attenuation factors, lead equivalents and radiation damage, the shielding designer will find useful information on physical and chemical properties, fabrication and on applications and design considerations. The materials considered comprise the seven most commonly used metals, soil, water and air, ceramics (bricks, tiles and special types), transparent materials and concrete. The latter is treated in very much greater detail, 190 pages being devoted to a very wide variety of types.

In the next section, materials are considered as shielding against neutrons and gamma radiation. Information is given for most of the previous materials and a number of additional ones likely to be connected with nuclear reactors. The three final sections are much shorter and treat laminated shields, the effect of heat on concrete and the optimal choice of shielding materials.

The book contains 344 tables and 323 figures. Each page shows where to find the appropriate list of references from which this extensive information has been drawn. The majority of the numerical information is given in metric units but, perhaps inevitably, much is in imperial or U.S. measures. In some places the reader is assisted by dual scales or conversion factors. The subject index at the end of the volume is valuable but not complete; for example, the information on build-up factors for radiation shielding glasses cannot be located using the index.

Attenuation factors and build-up factors for gamma radiation are usually given for monoenergetic radiation with relatively few energies below 1 MeV. Sometimes they are given for particular radioisotopes. There is only one reference in the index to X radiation though, in fact, there is a little more information than this.

Volume II of the Compendium will be of most use to designers of shielding for reactors and for some other high energy installations within the nuclear industry. There is in Volume III, which has already been reviewed in this journal, a section on the design and shielding of medical radiation rooms which includes some information on the attenuation of X and gamma radiation. For most purposes Volume III (or a less expensive publication such as I.C.R.P. Publication 21) will give all the information required by the shielding designer and only a limited number of specialists will need to look further. The specialist designer will find useful information on the effect of radiation on the viscosity of lubricating oils and on the properties of a wide range of plastics and rubbers; he may be disappointed not to find any information about "heavy metal" and the depleted uranium/molybdenum alloys used for source shielding or about gold and the low melting point eutectics used in patient protection moulds. There is relatively little attenuation data beyond 10 MeV and a lack of the special information sought by the designer of low background installations. Nevertheless the amount of information in the Compendium far exceeds that in any previous publication on shielding.

The contributions from so many sources have been very effectively brought together by the editors and the quality of production matches that of the previous two volumes (as does also the price).

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A computer-based technique for measurement of renal parenchymal area on intravenous urograms

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ABSTRACT

Accurate measurement of the renal parenchymal area of intravenous urograms is described using a graphic tablet with a pressure-sensitive surface linked on-line to a computer. The area outlined on the tablet is immediately computed and shown in square centimetres on a television screen and on a data print-out. The renal areas of 22 patients' urograms were studied before and three months after renal stone removal under local hypothermia. Renal function was measured by creatinine clearance. Conventional measurements of renal length, width and area were also performed for comparison. Results confirmed that while overall kidney size was reduced following operation, the parenchymal area and creatinine clearance were unaltered.

This computer-based technique is simple to perform, quick and accurate, and provides quantitative information on intravenous urograms.

The problem of measuring the mass of renal parenchyma by intravenous urograms is difficult, particularly where hydronephrosis or pyelonephritis cause gross distortion of the urinary collecting system. The length of the kidney by no means represents a measure of normal parenchymal volume or area, nor does measurement of renal width. The measurement of roentgenographic renal area was described by Moell (1961) using length × width to determine the renal area. The approximate area of a renal ellipse can be estimated using the formula $L/2 \times B/2 \times \pi$ (Blandy and Pead, 1967), but the size of the collecting system is not taken into account. Techniques for the subtraction of calyceal and renal pelvis areas involve the use of either the "counting squares" technique, or tracing the renal area onto cardboard, which is then cut out in the shape of the kidney and the collecting system, weighed and compared with the weight of a known standard area, to obtain the total parenchymal area (Griffiths *et al.*, 1975). The planimeter method of outlining the kidney and calyces has also been used to obtain the area (Moell, 1956; Blandy and Pead, 1967), but all these three methods are tedious, time-consuming and of doubtful accuracy.

A simple technique has been developed for measurement of the renal parenchymal area with direct reference to the shape and contour of the collecting system, using a computer.

METHODS

The system works by transducing to a computer the position of a pen pressed onto a pressure-sensitive surface as it is drawn round a curve, sampling the coordinates (X,Y) every four milliseconds. From this information, the area of the curve can be computed. The user is guided throughout the process by computer-generated messages on a television screen, and has options, *e.g.* to sum areas together or omit previously computed areas from a sum (by touching specially designated points on the surface), finally obtaining a total sum of areas, the mean, the standard deviation and the coefficient of variation. The graphic tablet with this pressure-sensitive surface (Quest Automation Ltd.) was linked to a Honeywell DDP-516 computer. The computer program used was developed for general-purpose area measurements.

A ten-minute intravenous urogram film with compression applied to the patient's abdomen was selected and the renal outline and calyceal pattern marked on the film with a pen (Fig. 1). A later film was used if there was a delayed excretion of contrast medium on those patients with poor renal function. A tracing was then made onto thin paper and the tracing placed onto the graphic tablet. The renal circumference and the calyceal pattern were then outlined with a ball-point pen (Fig. 2). The area of renal parenchyma was immediately computed and the area outlined shown in square centimetres on the television screen and on the data print-out. Ten tracings of the same X ray were used initially to determine the standard deviation of the method, and then each X ray in the series was outlined twice and the mean of the two readings recorded.

A retrospective study was performed measuring the renal parenchymal areas of the urograms of 22 patients undergoing the operation of nephrolithotomy under local hypothermia. Pre-operative and three month post-operative urograms were examined using the computer technique. The length and width of the kidney, deriving approximate renal

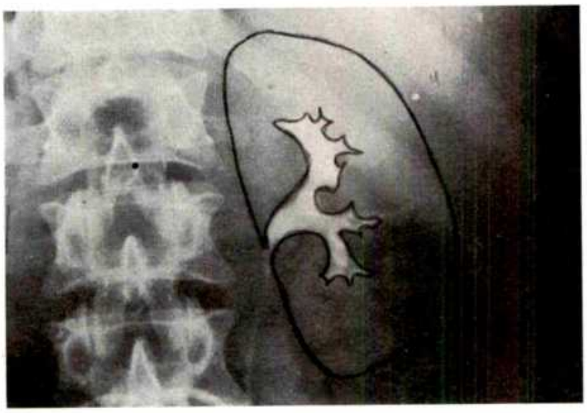

Fig. 1.
Intravenous urogram with renal border and calyceal pattern outlined.

area (length × width), were also measured with a ruler. Creatinine clearance estimations were performed before and three months after surgery, using the mean of two consecutive 24 hour urine collections and one plasma creatinine on each occasion. The results were statistically analysed using paired t-tests.

Results

The computed parenchymal areas were expressed in square centimetres and the creatinine clearances in ml per minute (Table I). The mean renal length, width and areas of the same patients are shown in Table II, with their differences between post- and pre-operative values. The accuracy of the computer method was initially evaluated using ten measurements of the same X ray. The mean parenchymal area of the test X ray was 62.8 cm^2, with a standard deviation of 0.2 cm^2, the coefficient of variation being 0.3%. The mean increase in renal parenchymal area from before nephrolithotomy to three months after (Table I) was not statistically significant ($p > 0.05$). The mean relative increase (12%) was just significant at the 5% level. The mean increase in creatinine clearance was not significant but the mean relative increase (22%) was just significant at the 5% level. No correlation could be demonstrated between a rise or fall in creatinine clearance and an increase or decrease in renal parenchymal area.

Using conventional measurements (Table II), the mean decrease in length of 0.5 cm was just significant ($p=0.05$). The width measurements showed no significant difference but the approximate roentgenographic area (length × width) was significantly smaller after surgery at a mean of 6.4 cm^2 ($p < 0.05$). None of the mean relative differences was significant at the 5% level.

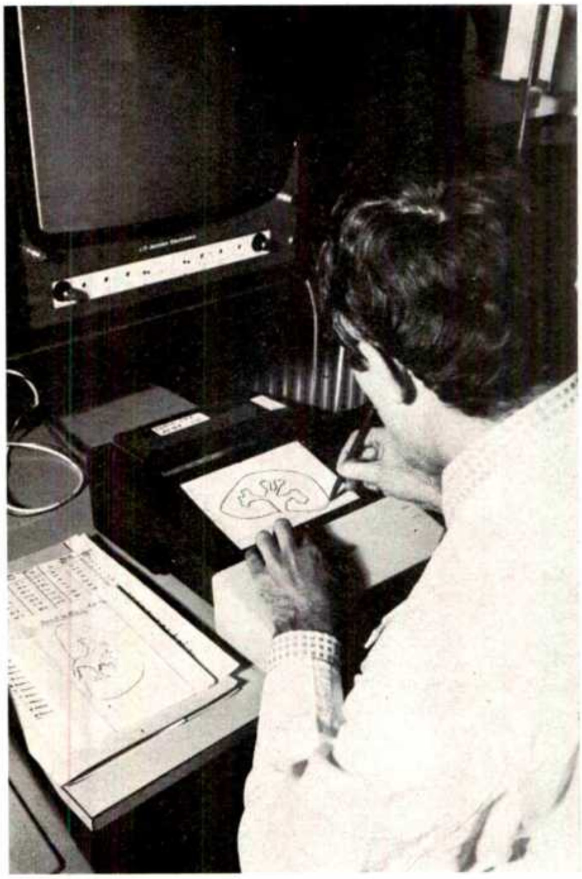

Fig. 2.
Using the computer-linked graphic tablet.

Discussion

From the radiologist's viewpoint, the fact that kidneys look smaller, and in fact are estimated as smaller when using length and width as the parameters, can lead to misleading conclusions. In this series, the parenchymal area was not reduced despite the overall reduction in the total size of the kidney. This reduction was almost certainly due to reduction in size of the collecting system. While there may be only a little variation in the relative area and volumes of the calyces in normal subjects, this is not true for patients with stone disease. The contorted urograms of such patients are extremely difficult to assess visually and random measurements of cortical thickness are inadequate. Hence the importance of measurement of parenchymal area. The surgeon's problem of whether nephrolithotomy

TABLE I

COMPUTED RENAL PARENCHYMAL AREAS AND THE CORRESPONDING CREATININE CLEARANCES OF 22 PATIENTS

Patient number	Computed renal area (cm^2)			Creatinine clearance (ml/min.)		
	Pre	Post	Difference	Pre	Post	Difference
1	68.2	61.7	− 6.5	68	75	+ 7
2	57.6	65.8	+ 8.2	110	107	− 4
3	32.4	48.7	+16.3	49	52	+ 3
4	29.4	51.4	+22.0	72	79	+ 7
5	41.1	48.5	+ 7.4	51	52	+ 1
6	52.8	51.9	− 0.9	69	54	−15
7	62.7	78.6	+15.9	88	128	+30
8	45.4	71.7	+26.3	16	41	+25
9	42.0	42.6	+ 0.6	72	79	+ 5
10	62.8	61.0	− 1.8	101	113	+12
11	26.9	27.2	+ 0.3	14	30	+16
12	37.2	31.4	− 5.8	106	74	−32
13	41.6	50.5	+ 8.9	91	80	− 9
14	57.6	73.1	+15.5	100	81	−19
15	37.5	43.8	+ 6.3	83	86	+ 3
16	70.3	54.5	−14.8	92	126	+34
17	78.3	67.1	−11.2	100	108	+ 8
18	42.5	34,8	− 7.7	97	108	+11
19	58.4	56.1	− 2.3	46	112	+66
20	67.5	54.5	−12.0	75	78	+ 3
21	46.5	45.3	− 1.2	42	34.5	− 7.5
22	29.9	47.5	+17.6	27	36	+ 9
Mean ± S.E.M.	49.5 ± 2.9	53.1 ± 2.8	+3.7 ± 2.5	71.3 ± 6.2	78.8 ± 6.2	+7.0 ± 4.3
Mean Relative Difference* ± S.E.M.			+12% ± 6%			+22% ± 11%

*Defined as (Difference)/(Pre-operative Value) and expressed as a percentage.

TABLE II

CONVENTIONAL MEASUREMENTS OF RENAL LENGTH, WIDTH AND AREA IN THE SAME 22 PATIENTS

	Length (cm)		Width (cm)		Area (cm^2)	
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative
Mean ± S.E.M.	13.4 ± 0.3	12.9 ± 0.3	7.2 ± 0.2	7.1 ± 0.2	98.1 ± 5.3	91.7 ± 4.2
Mean Difference* ± S.E.M.	−0.55 ± 0.25		−0.15 ± 0.13		−6.4 ± 3.0	
Mean Relative Difference† ± S.E.M.	−3.5% ± 2.0%		−1.7% ± 1.7%		−4.9% ± 3.0%	

*Defined as Post-operative − Pre-operative.

†Defined as (Difference)/(Pre-operative Value) and expressed as a percentage.

causes the kidney to shrink, ischaemia causing possible reduction in renal substance, can be investigated by this technique.

In our series neither renal parenchymal area nor creatinine clearance were reduced by nephrolithotomy under hypothermia. If anything they are improved by the de-stoning. These results challenge the theory of ischaemic parenchymal shrinkage following hypothermic surgery.

It has been shown in normal adults that there is a clear correlation between renal size and glomerular filtration rate, big kidneys having a larger G.F.R.

than small (Andersen and Mogensen, 1973). In disease, the total renal size cannot be related directly to function, especially in urinary systems obstructed by calculi or affected by infection. While it is interesting to note that the kidney has become smaller in pyelonephritis or ageing (Griffiths *et al.*, 1976), or larger following contralateral nephrectomy (Dossetor, 1975), or altered during transplant rejection (Fletcher and Lecky, 1969), unless calyceal size is taken into account, the measurements are of limited value. The relationship between renal function as measured by creatinine clearance and renal parenchymal size in our patients was vague to say the least. When individual changes in parenchymal size were compared with their own changes in function before and after surgery, no significant correlation could be demonstrated. Four of the 22 patients had solitary kidneys but even in these, no better correlation between change in area and function could be demonstrated.

The post-operative mean rise in clearance of 7 ml per minute was not significant (though the mean relative rise was just significant at the 5% level), but when the post-operative clearances of 100 patients were studied of which these 22 were a random sample, the rise in creatinine clearance was significant (Wickham *et al.*, 1974).

The computer technique for measurement of the parenchymal area is an improvement on present methods of assessment. It is simple and gives immediate quantitative results. It is perhaps worth noting that with only ten minutes' practice, a clinician without computer training was able to use the technique with ease. We suggest that if a university or hospital has a computer freely available then this method is worth investigating.

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Book review

The renal uptake of radioactive mercury (^{197}Hg Cl_2). Edited by C. Raynaud, pp. 211, 102 figs., 47 tables, 1976. (Springfield, Charles C. Thomas; American Lecture Series), $22.75.

This comprehensive multi-author monograph gives an account of knowledge of the uptake of the inorganic mercury compound ^{197}Hg Cl_2 by the kidney and its use with external counting techniques. The localization of ^{197}Hg Cl_2 to the cortex, probably to the pars recta of the proximal tubule, is used as a basis of an individual function test that is complementary to radiological findings. Methods for correcting for the liver uptake in relation to the right kidney, for the depth of the kidneys and for circulating and intestinal radioactivity are described. The relationship between the results of the test and conventional clearance methods are detailed but there is no comparison made with studies using radioiodinated Hippuran. Only one reference is more modern than 1972. The book describes an interesting technique of measuring individual renal uptake function. It further demonstrates the need for measuring the contribution of a diseased kidney to total renal function before nephrectomy is contemplated.

K. E. BRITTON.

1976, *British Journal of Radiology*, *49*, 840–851

Combination of isotope venography and lung scanning

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ABSTRACT

Seventy patients were investigated by isotope venography of the lower leg veins and pelvis using ^{99}Tc^{m} human serum albumin, mainly as microspheres, in the course of routine lung scanning.

In 54 of these patients, 52 pelvic, and 98 conventional ascending X-ray contrast venograms were performed for comparison, ninety three per cent showed good correlation, and 4% poor correlation. There were 2% false positive and 1% false negative isotope examinations.

Isotope venography proved to be a painless, safe and reliable method for the detection of deep vein thrombosis. Its correlation with contrast venography is high, especially for the upper thigh and pelvis. It can be performed in 30 minutes, including standard lung scan, and can be repeated in patients to assess response to treatment, saving the patient the discomfort and radiation of comparable radiological examinations.

Isotope venography for the detection of deep vein thrombosis was introduced in 1969 by Webber *et al.* and is based on his observation that isotope uptake was occasionally seen in the axillary region of patients after injection for conventional lung scan. It was noted that nearly all these patients had been recently subjected to axillary vein catheterization for intravenous therapy and it was thought that in these areas of increased uptake, "hot spots" were due to the trapping of albumin aggregates in clots formed on areas of injured endothelium. This suggested that, by injecting the isotope for conventional lung scan into the dorsum of the feet, useful information could be obtained about the deep venous system of the legs, and encouraging results have been reported. The purpose of this study is to establish the value of isotope venography for the detection of deep vein thrombosis.

MATERIALS AND METHODS

Seventy patients referred to the Clinical Scanning Unit or Diagnostic X-ray Department of Aberdeen Royal Infirmary with the provisional diagnosis of pulmonary embolism or deep vein thrombosis, or both, were examined by combined isotope venography and lung scan.

The technique of isotope venography was, with some modification, based on that described by Rosenthal and Greyson (1970) and Yao *et al.* (1973). One mCi of ^{99}Tc^{m} human serum albumin as macroaggregates or more often, microspheres, was diluted in 20 ml of saline and equal divided doses injected simultaneously into a dorsal vein in each foot below ankle tourniquets. Blood pressure manometer cuffs were applied above the knee to delay the flow of isotope through the deep venous systems sufficiently to allow adequate count collection. During the injection, a 50-second exposure was performed with a gamma-camera over three successive areas, calf, thigh and pelvis, and the information stored on magnetic tape. Scintiphotos on Polaroid could then be obtained by replay when convenient. Standard lung scan views were then performed. Finally, the calfs, thighs and pelvis were again examined by imaging each area for 100 seconds. The isotope venogram therefore comprised an initial dynamic and a second static phase. The patients were then transferred to the X-ray Department for ascending and pelvic contrast venography, which at that time was the routine procedure in the investigation of thrombo-embolic disease in this hospital.

CRITERIA OF NORMAL ISOTOPE VENOGRAM

The criteria of normal isotope venography were as follows:

(a) *Dynamic phase* (Figs. 1A and 2A).
Following the injection into dorsal veins of the feet in a normal patient, there is a continuous flow of isotope from the ankle up to the inferior vena cava. Individual veins in the calf cannot be identified.

(b) *Static phase* (Figs. 1B and 2B).
There is evidence of some background radioactivity due to free technetium pertechnetate and small aggregates of labelled albumin, not trapped in the lung capillaries. No "hot areas" are seen apart from the bladder region, due to excreted radioactivity.

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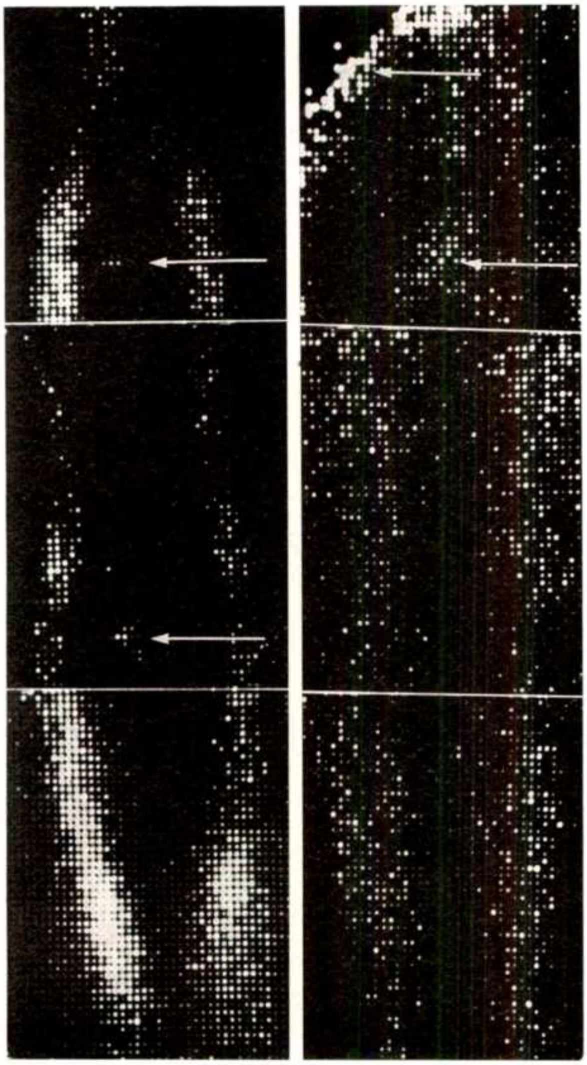


A B

Fig. 1.

Normal isotope venogram. (a) dynamic and (b) static phase. The arrows in (a) show the level of the knees and symphysis pubis marked by an isotope source. The upper arrow in (b) indicates a common gamma-camera artefact due to the margin of the crystal, and the lower increased concentration of the isotope in the bladder.

Criteria of a Pathological Isotope Venogram

1. *Dynamic phase.*

When thrombi are present, there is delay in the flow rate of the isotope. With occlusion of the deep venous system of the legs or the main veins of the pelvis, isotope passage through the superficial venous system or collateral channels is noted (Fig. 3).

In the presence of varicose veins (Fig. 4a) there is irregularity of the isotope pattern.

2. *Static phase.*

The main abnormalities demonstrated are "hot spots" which indicate fresh thrombi (Figs. 5, 6, 7, and 8).

When long venous segments are occluded by thrombi, generalized increase in radioactivity can be seen (Fig. 9).

Other causes of increased radioactivity have been collected. These include:

(1) Venous stasis in varicose veins.
(2) Trapping of the aggregates
  (a) behind large valves
  (b) by a venous occlusion with poor collateral circulation.
(3) Recent venous injury due to:
  (a) venous catheterization
  (b) contrast venography.
(4) Superficial isotope contamination.
(5) Bladder accumulation of excreted radioactivity.

Results

In the 70 patients examined with isotope venography, a total of 52 pelvic and 98 ascending X-ray contrast venograms were available for comparison. Results were compared for (a) the detection of thrombi and (b) occlusion of the venous system with or without collateral circulation.

Correlation was assessed as good when normal and abnormal areas as indicated on the X-ray contrast venogram could be clearly seen on the isotope venogram. Correlation was adjudged poor when isotope demonstration was indistinct or doubtful. The result was noted as false positive when the isotope venogram demonstrated a lesion in an area clearly normal on the X-ray examination and a false negative, when a clear X-ray lesion was massed on the isotope examination.

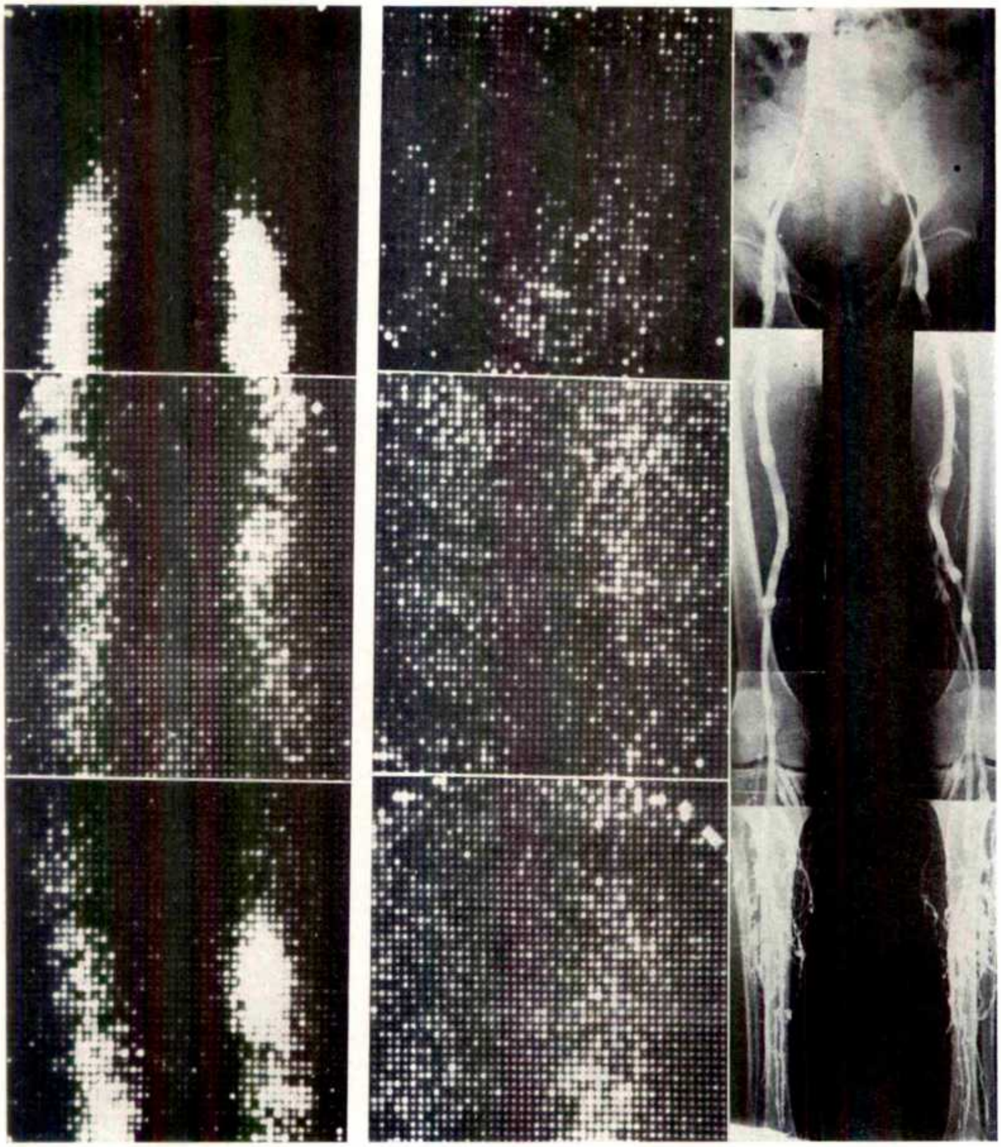
The examinations were read blind independently by two radiologists.

The results produced good correlation 93%, poor correlation 4%, false positive 2%, false negative 1%.

Tables I, II and III, show in detail the results divided into regions—pelvis, thigh and calf. There was complete correlation between X-ray and isotope examination in the pelvis and the poorest correlation in the calf.

Discussion

A diagnostic examination to detect deep venous thrombosis in the legs should be safe, accurate, easily performed, and cause minimal patient discomfort. If it is to be applicable to a large number of patients in a general department, it must be inexpensive, reasonably rapid, and involve a minimum of trained staff.



A B C

FIG. 2.

Normal isotope (A), (B) and (C) the corresponding conventional bilateral ascending and pelvic venograms.

TABLE I

PELVIC REGION—CORRELATION BETWEEN ISOTOPE AND X-RAY CONTRAST VENOGRAPHY IN 52 PATIENTS

Isotope venogram	Contrast venogram	Number of patients
+	+	13
—	—	39
+	—	0
—	+	0
Total		52

TABLE II

THIGH REGION—CORRELATION BETWEEN ISOTOPE AND X-RAY CONTRAST VENOGRAPHY IN 98 EXAMINATIONS

Isotope venogram	Contrast venogram	Number of examinations
+	+	24 (poor correlation in 4)
—	—	71
+	—	3
—	+	0
Total		98

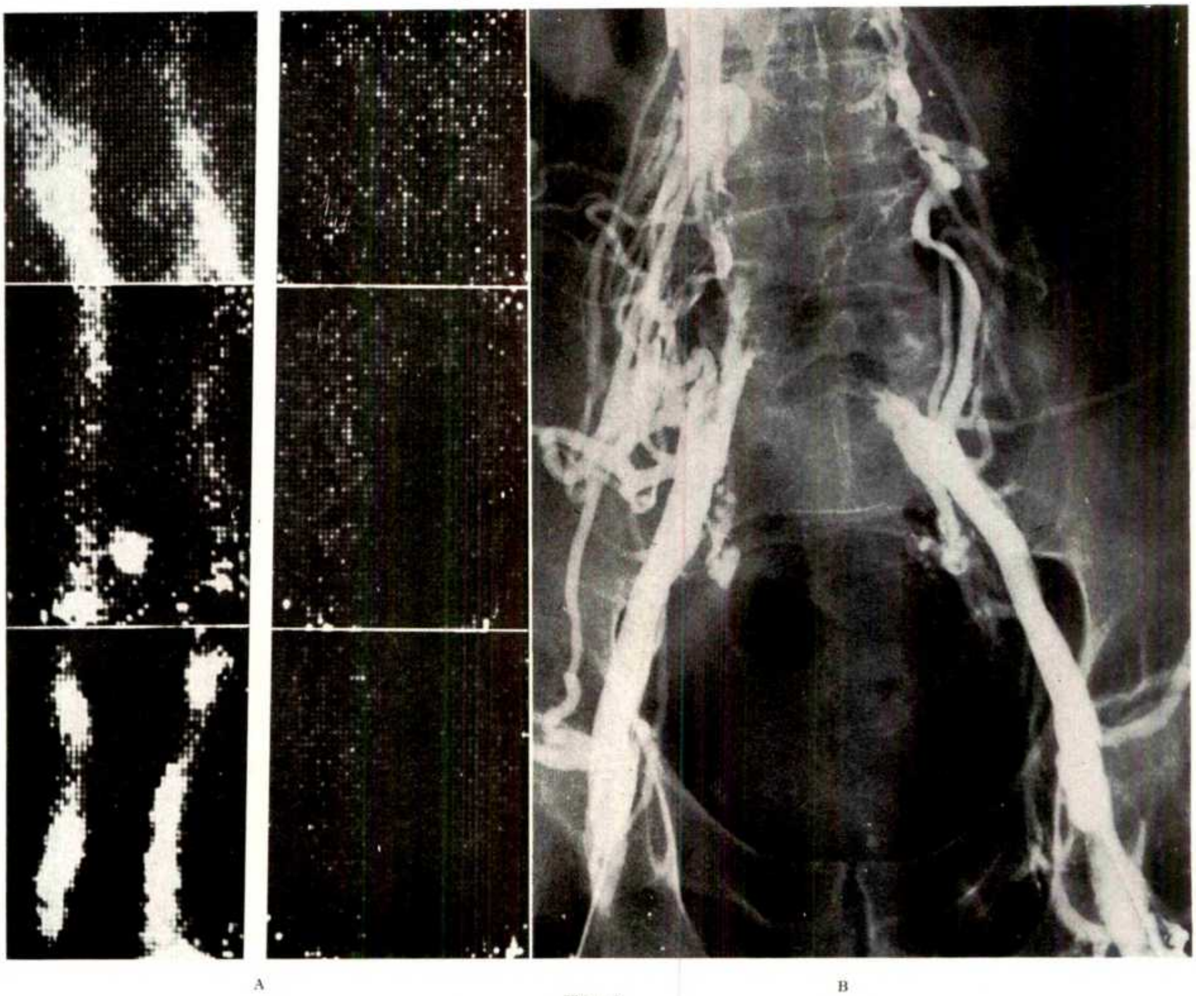


FIG. 3.

Obstruction of the I.V.C. with collateral circulation (A). (B) corresponding contrast pelvic venogram.

TABLE III

CALF REGION—CORRELATION BETWEEN ISOTOPE AND X-RAY CONTRAST VENOGRAPHY IN 98 EXAMINATIONS

Isotope venography	Contrast venography	Number of examinations
+	+	34 (poor correlation in 6)
—	—	59
+	—	3
—	+	2
Total		98

X-ray contrast venography can be extremely painful, occasionally produces an allergic reaction and even phlebitis, and can be difficult to interpret.

^{131}I fibrinogen is not accurate enough in the upper thigh and pelvic region and produces false positive results in the presence of an haematoma. Further, the results are not available for 24–48 hours or more and are less accurate the older the thrombus.

Ultrasonic techniques only detect non-occlusive thrombi where the blood flow is materially affected. False results are also obtained where there is complete occlusion with a rich collateral circulation.

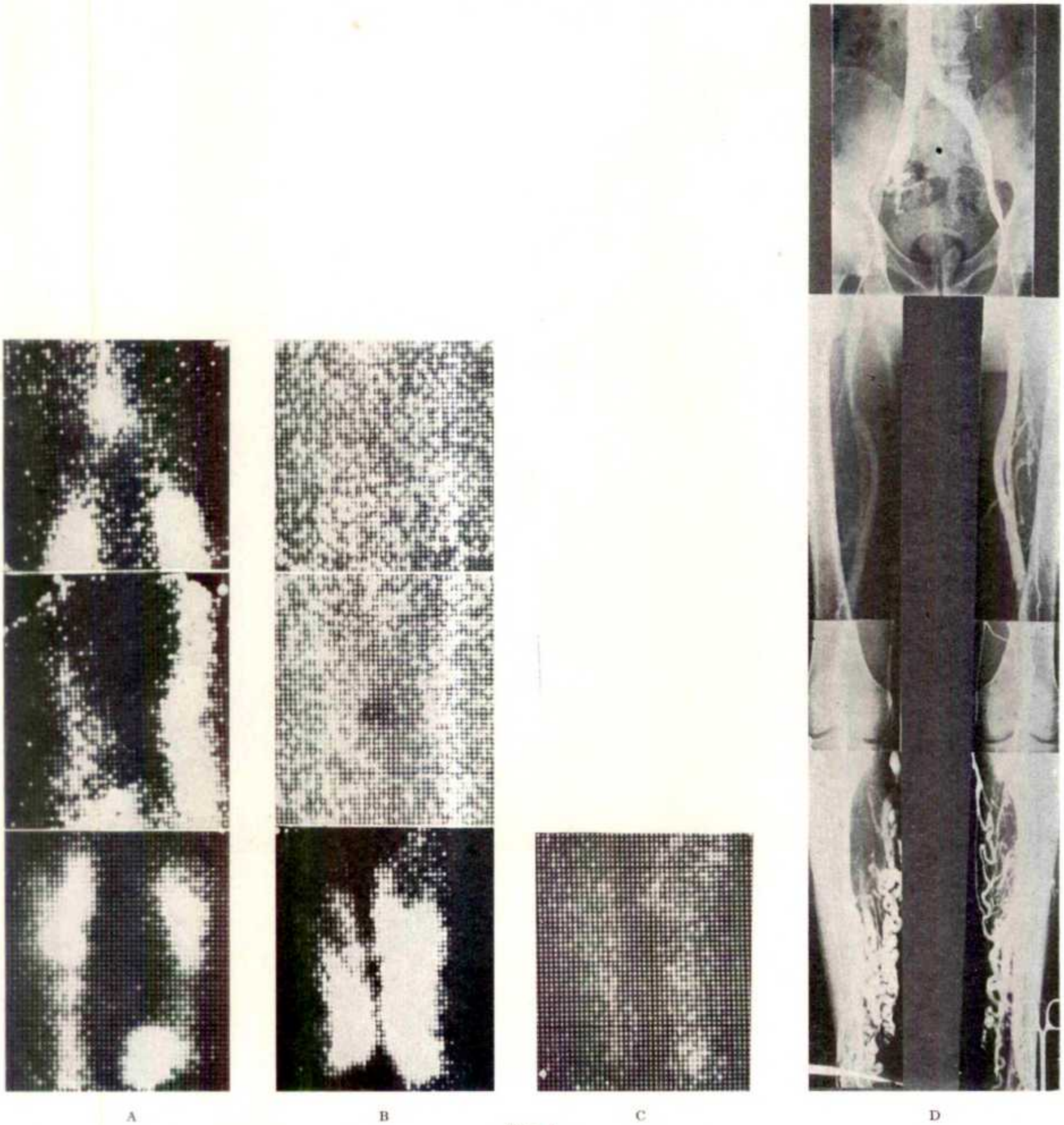


Fig. 4.

Dynamic phase (A) irregular column of isotope in both calfs and right lower thigh. Static phase (B) increased activity in the calf regions disappearing after mild massage. (C) Contrast venogram. (D) Shows varicose veins.

Isotope venography is easily performed. It causes much less discomfort to the patient than X-ray contrast venography. The results are immediately obtained. It is superior to ^{131}I fibrinogen for the upper thigh and pelvis and is not affected by the presence of a soft tissue haematoma. Non-occlusive thrombi are easily detected because of the large area of contact of the isotope preparation with the thrombus. The resultant lung scan is uncompromised and the examination can be repeated in the follow up of treatment without exposing the patient to the discomfort or the higher radiation dose level of repeated contrast venography.

This series records the largest number of comparative ascending contrast venograms and is the first with adequate comparison with X-ray contrast pelvic

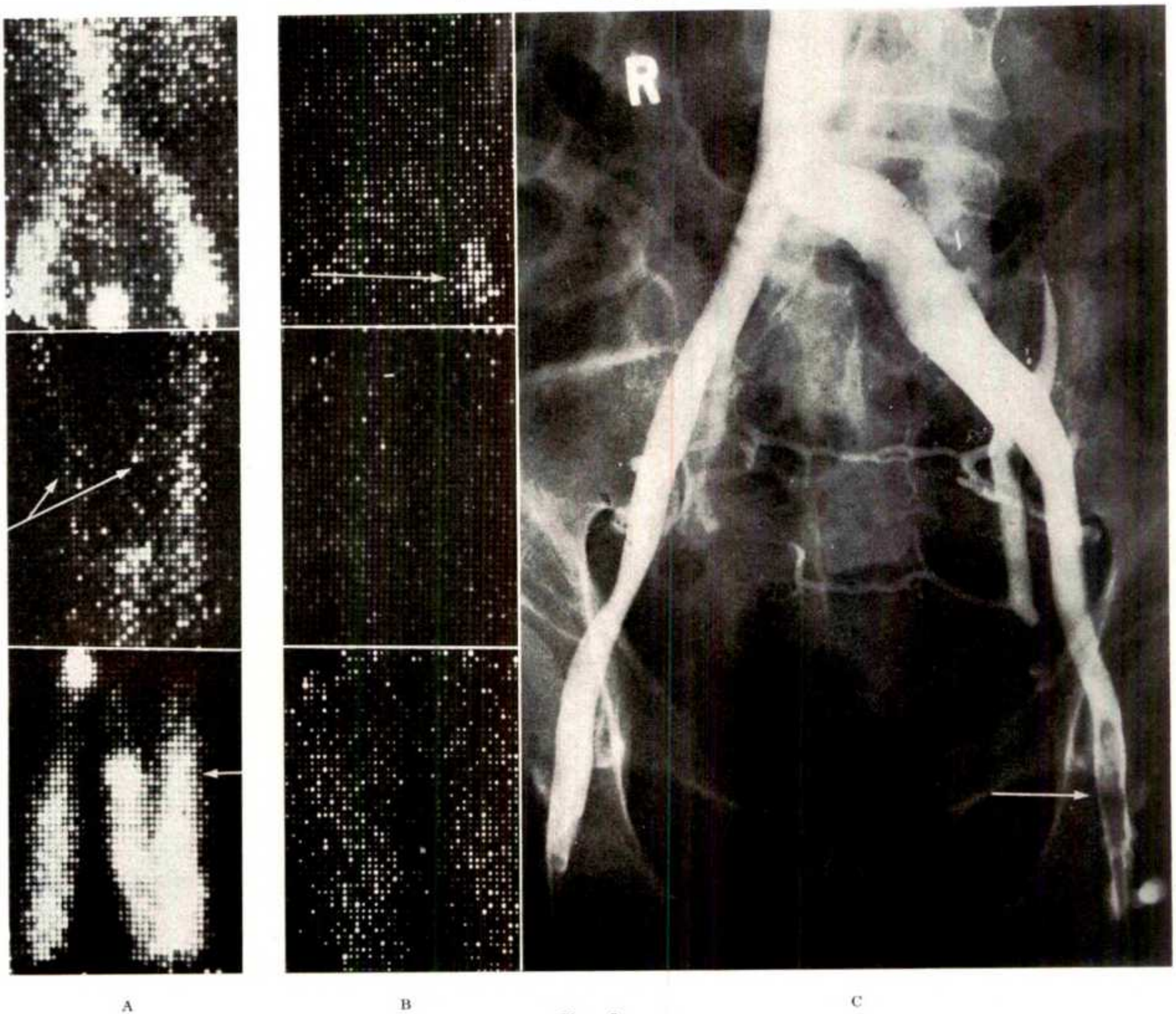


FIG. 5.

Dynamic phase (A). The deep venous system of the right leg is not visualized due to previous ligation. The long saphenous on both sides (double arrow) and the deep venous system of the left leg (single arrow) are well seen. Static phase (B) "hot spot" in left groin (arrow) indicating fresh thrombus. Conventional pelvic venogral (C) confirms.

venograms which are necessary for the detailed demonstration of the ilio-femoral segments, and were available in 75% of the present series.

The overall correlation between the isotope and contrast venograms is comparable to that reported by Yao *et al.* (1973) and Duffy *et al.* (1973) but slightly poorer than Henkin *et al.* (1974) who reported 96% good correlation, but only in 23 patients.

We confirm the observation of previous workers that the accuracy of this technique is poorer in the calf, but cannot confirm the findings of Rosenthal and Greyson (1970) who reported false positive results in nearly 70% of their leg examinations. Most of the false results in this series were obtained in the early examinations and became less frequent with experience. The false positive results seem to be produced by trapping of the isotope behind large valves (Fig. 10) and stasis in varicose veins. Ryo *et al.* (1975) suggested that turbulent flow behind large valves caused the isotope accumulation and found no difference between macroaggregates and microspheres. They also carried out microscopic examinations which did not show any albumin adherence

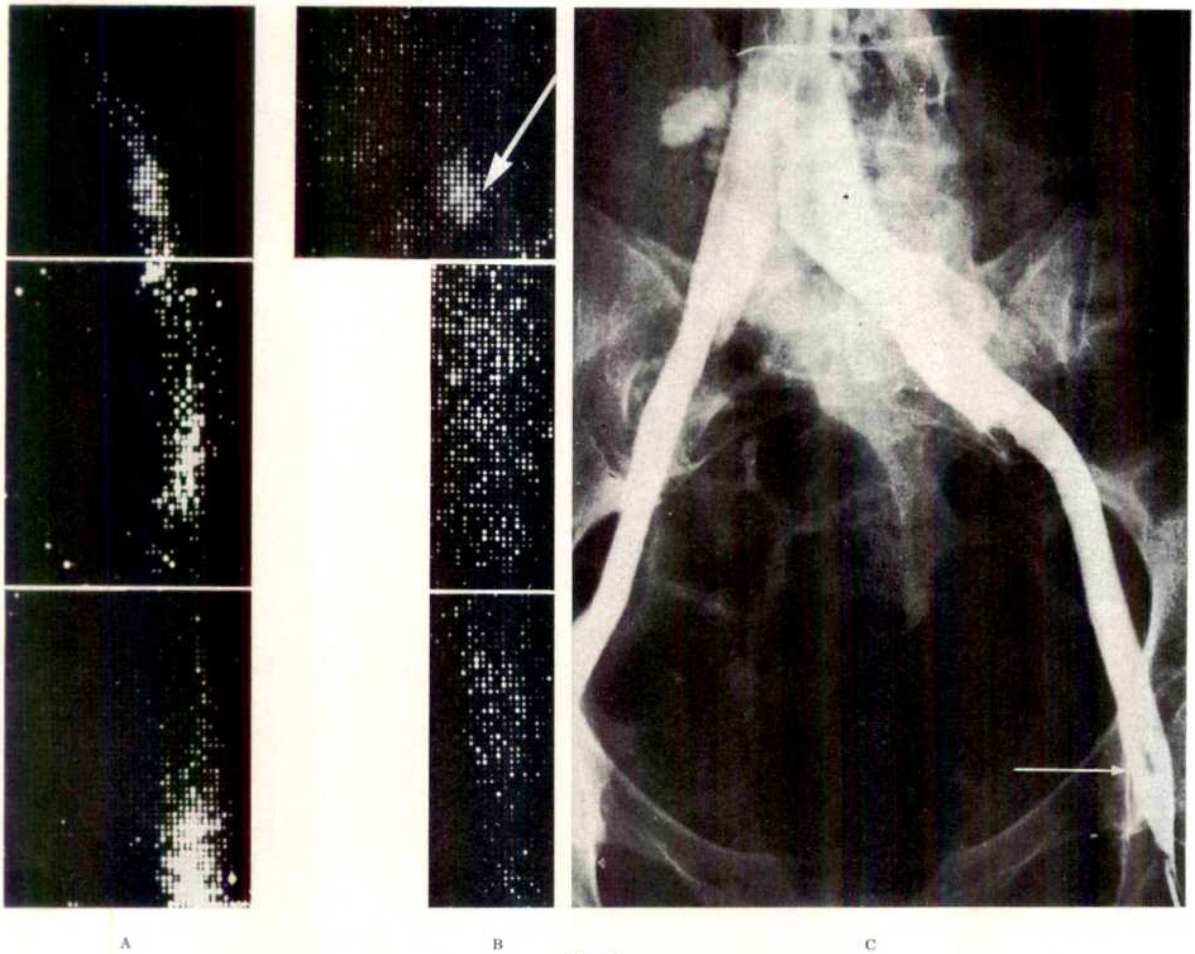


FIG. 6.

Dynamic phase on left leg normal (A). Static phase (B) "hot area" in left groin (arrow). The pelvic venogram (C) confirms the presence of a non-occlusive thrombus (arrow).

to the valves. This latter observation is contrary to the experience of Yao *et al.* (1973) and with our findings that the false positive results caused by large valves occurred mainly with macroaggregates in the first ten cases. No false positives were noted after the introduction of microspheres. Perhaps the spherical shape of the microspheres reduces their tendency to valvular adherence, as has been suggested by previous authors. The use of microspheres, and the improved trapping in the pulmonary capillaries, has also reduced the background irradiation.

When there was clinical evidence of varicose veins, the application of crêpe bandages, elevation of the leg, mild massage and then repeat examination in the suspicious area, resulted in elimination of false positives. This mild massage had no effect on uptake due to a thrombus.

Of the two false negative results, one was due to insufficient pressure of the cuff around the ankle joint, allowing the isotope to escape through the superficial system, and the other was due to complete occlusion with large collateral formation where the isotope by-passed the thrombus and did not in fact make contact with a large area of it.

The mechanism of thrombus localization is not completely understood. The most likely explanation

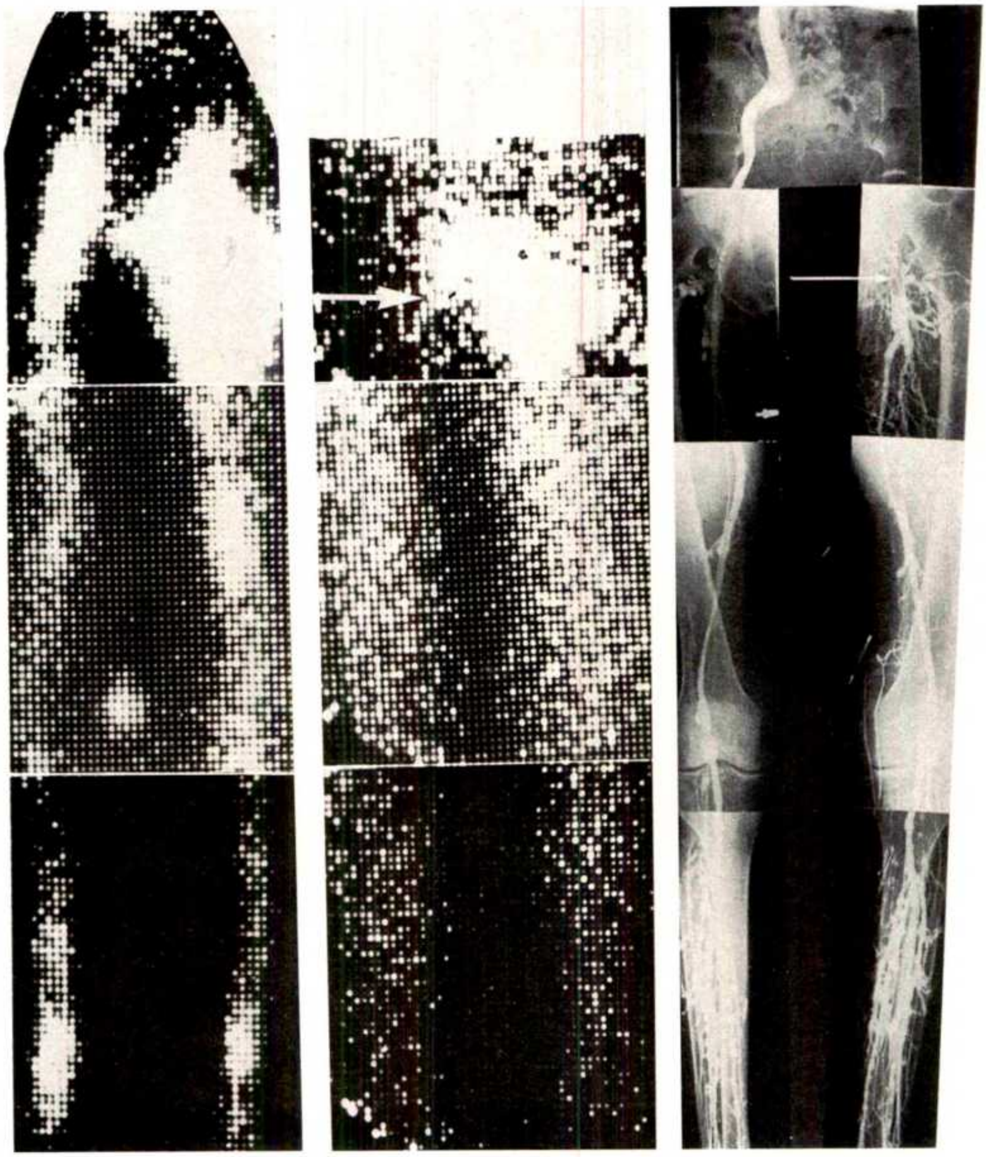
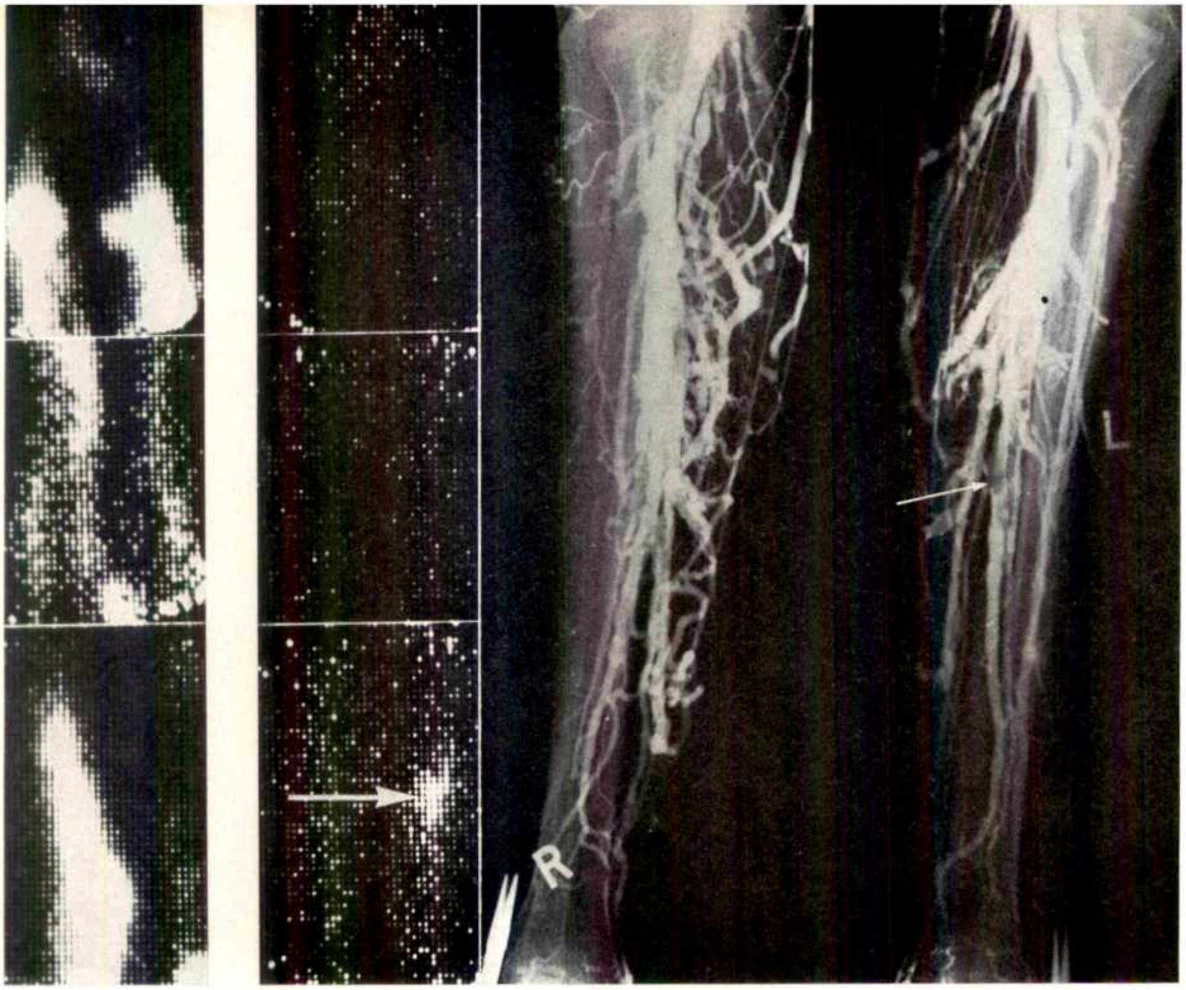


Fig. 7.

Dynamic phase. (A) Complete occlusion in the left groin. Static phase (B) increased activity (arrow) indicating fresh thrombi. Contrast venogram (C) showed the presence of thrombi (arrow). Attempt to cannulate the left femoral vein on the groin was unsuccessful.

is the entrapment of human serum albumin macroaggregates or microspheres by fine filaments extending from the surface of the clot. Webber *et al.* (1971), after experimenting with clots formed in a haemocytometer chamber, noticed that suspended particles of human albumin formed a "stand-off zone" around the clot and concluded that, apart from mechanical trapping, there must also be some electrostatic attraction between the clot and the particles. When some particles are attached to or attracted by the clot, further particles aggregate. Ryo *et al.* (1973)), failed to demonstrate any increased concentration of isotope in thrombi or areas of injured veins in scintigrams of isolated and emptied veins. They



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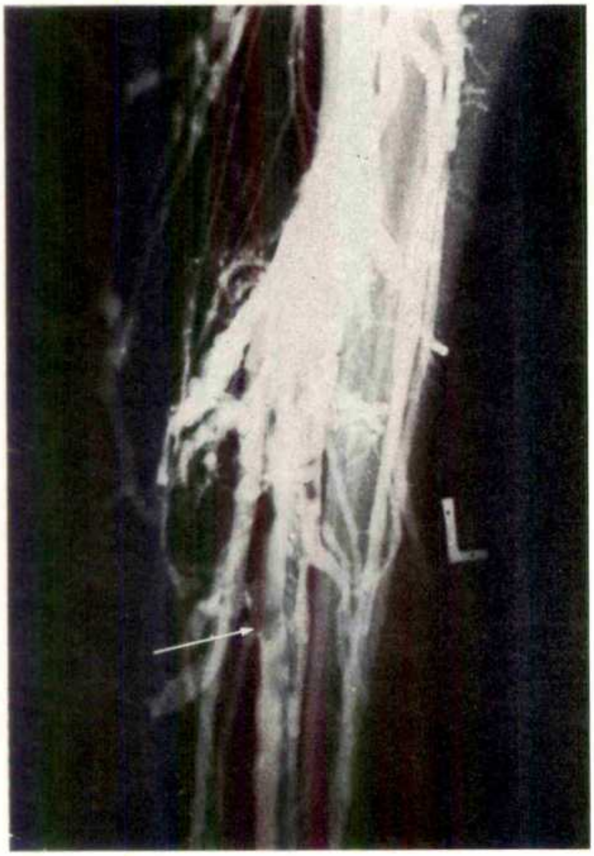

FIG. 8.

(A) "Hot area" static phase in the left mid calf region.

(B) Ascending contrast venograms—thrombus in the left calf region (arrow).

(C) Magnified view.

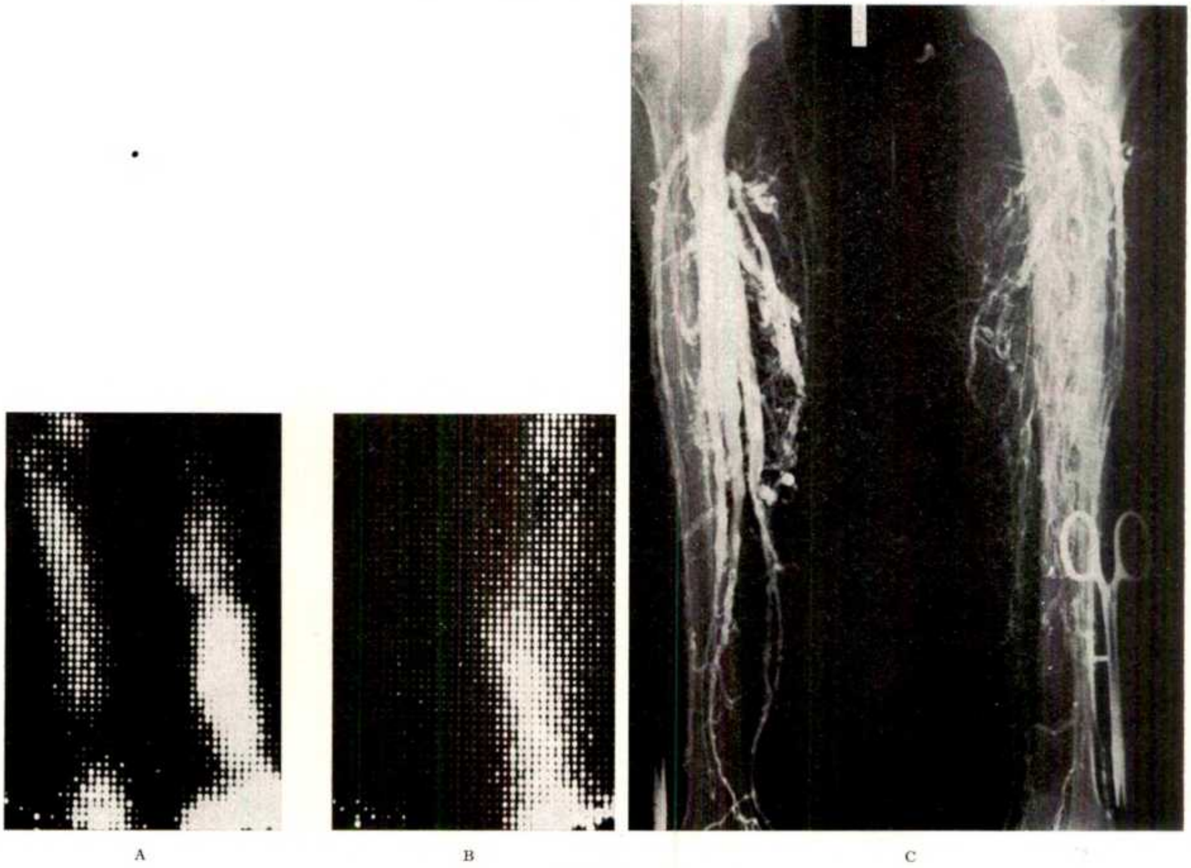

Fig. 9.

(A) Calf region of a normal dynamic phase and (B) static phase, increased activity in the whole length of the left calf. (C) Bilateral ascending venograms confirm the presence of extensive thrombi.

also found no evidence of macroaggregates to microspheres on the surface of thrombi or crush injured areas of veins in microscopic examination. They suggested turbulent flow as the cause of slow clearance of the isotope preparation near the area of thrombus or injured vein *in vivo* and suggested that the isotope had no real affinity to the thrombus. This is contrary to the finding of this series and of others. We noted that the increased uptake in the areas of recent venous injury or thrombi, persisted when imaging was repeated one hour or more after the original examination. It was also noted that massage failed to dissipate the isotope concentration and Fig. 11 demonstrates a case where isotope venography was performed 48 hours after bilateral femoral vein injections for X-ray contrast venography. This clearly shows persistent increased uptake at the venous puncture sites.

Different injection techniques reported in the literature were considered, including the injection of small volumes or washing the isotope preparation through with 2–4 ml of saline, Duffy *et al.* (1973) and Henkin *et al.* (1974), but none was found to be satisfactory. The present technique of isotope preparation dilution in 20 ml of saline produces a rapid continuous flow and appears to avoid false negative results due to excessive dilution. The problem of settling of the microspheres in solution was avoided by mild agitation of the vial and syringes before and during injection.

Isotope venography is a relatively new method and further studies are required particularly to investigate the mechanism of thrombus localization and to improve results. X-ray contrast venography which is the currently most widely used examination for the detection of deep vein thrombosis is far from

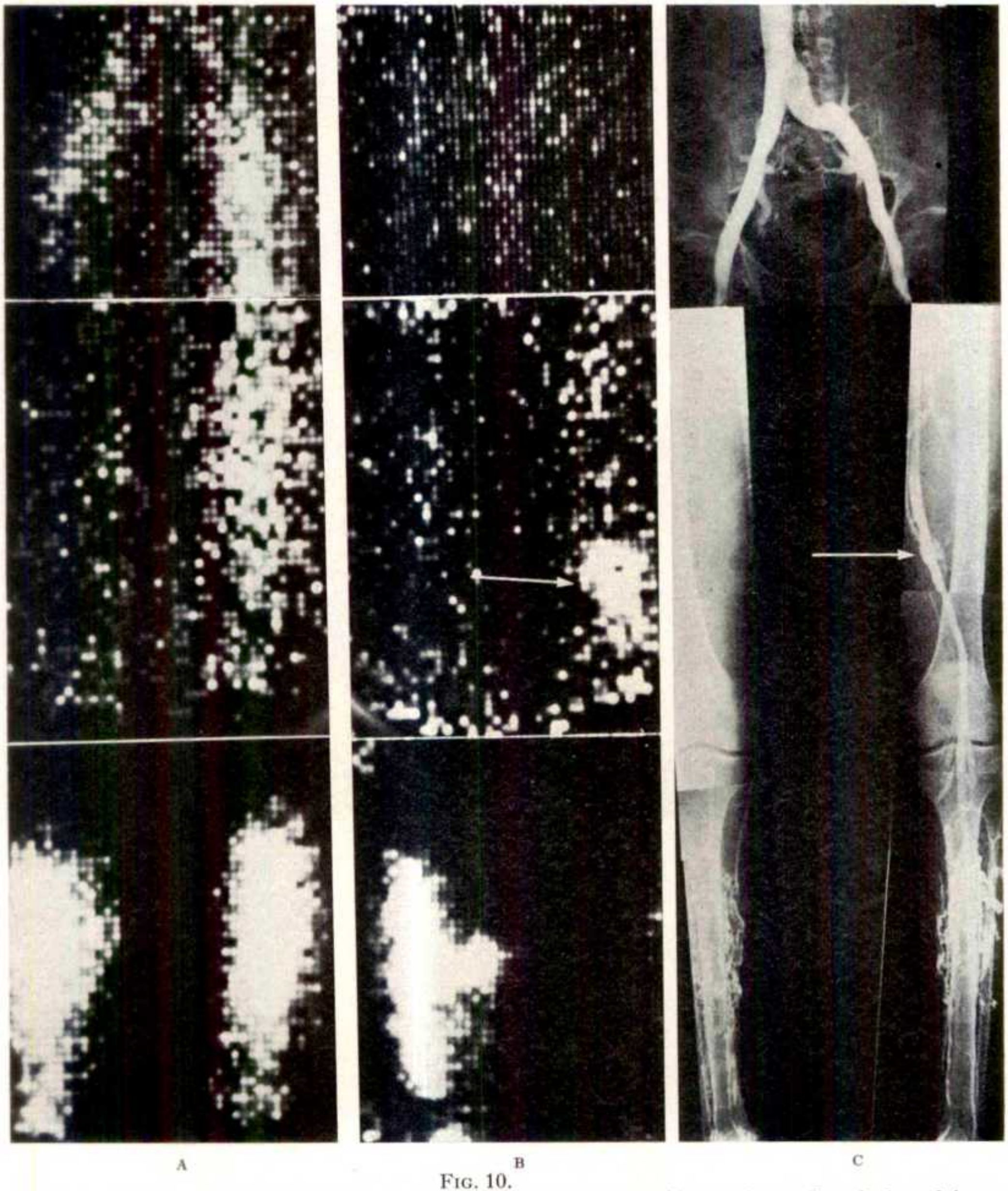

FIG. 10.

(A) The isotope columns in the dynamic phase are wider than usual because of incomplete cuff occlusion of the superficial venous system.

(B) Static phase. Increased activity in right calf region and a smaller one in the left lower thigh (arrow).

(C) Contrast venograms confirmed the presence of extensive thrombi in the right calf. The hot area in the left lower thigh in the isotope venogram was probably due to trapping of the isotope behind the valve in the femoro-popliteal region (false positive).

ideal because of technical considerations and the inevitable patient morbidity and irradiation. We consider that isotope venography, even in its present stage of development, can be considered as a safe and reliable substitute.

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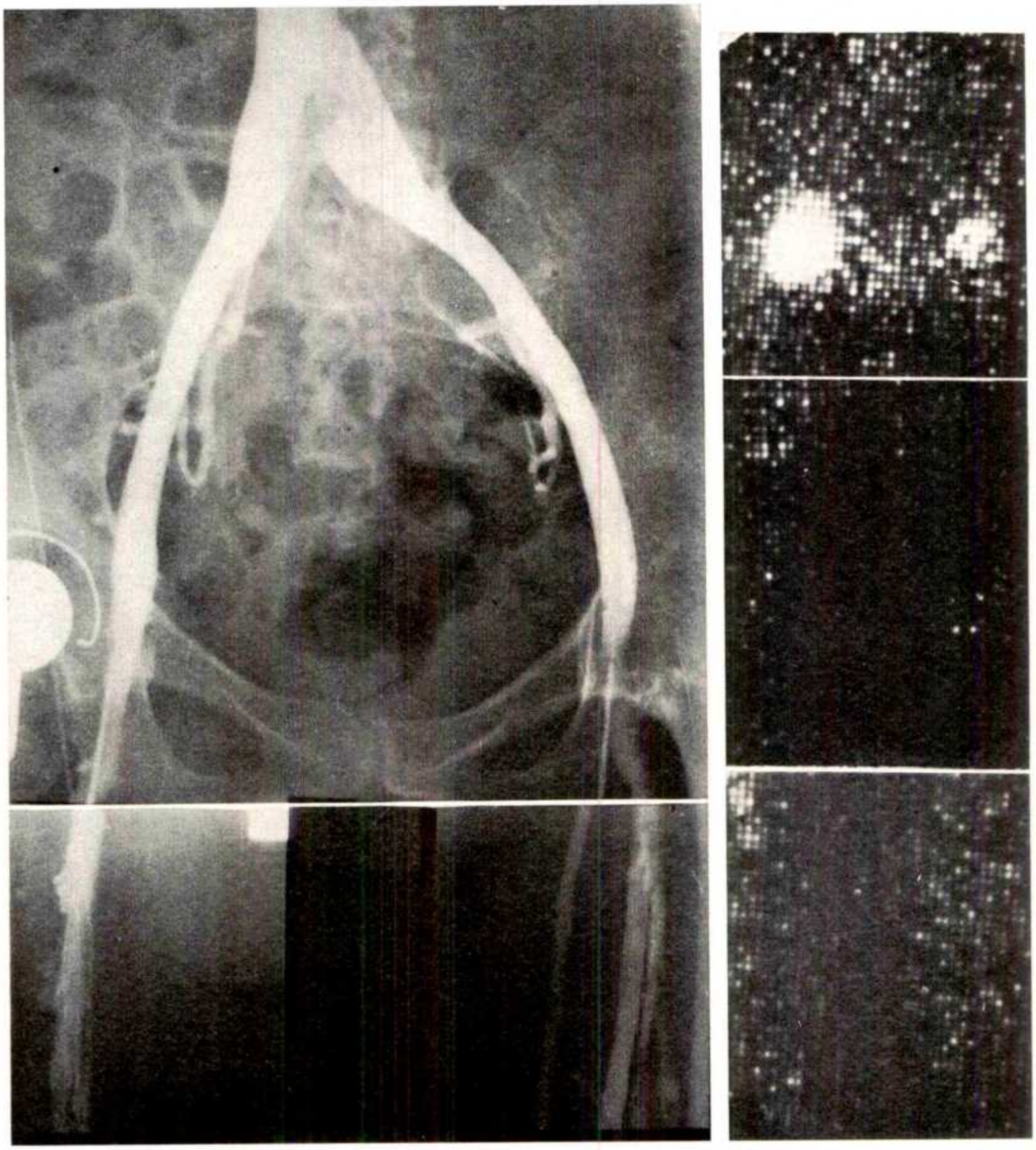

Fig. 11.

(a) Normal contrast venogram. (b) Static phase of isotope venogram performed 48 hours after the contrast venogram. The increased concentration in the ilio-femoral regions was due to the venous injury from the recent punctures (false positive).

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Liver and gall-bladder imaging with Technetium-99m dihydrothioctic acid and Technetium-99m pyridoxylidene glutamate – a study in the young pig

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ABSTRACT

Seventeen scans on ten young pigs were performed after injection of Technetium-99m labelled dihydrothioctic acid (^{99}Tc^{m}-DHT) and Technetium-99m labelled pyridoxylidene glutamate (^{99}Tc^{m}-PG) using a gamma-camera. Sequential images of the liver, gall-bladder and intestine were observed in all healthy animals. ^{99}Tc^{m}-DHT produced the clearer liver images, whereas ^{99}Tc^{m}-PG produced more rapid and intense gall-bladder images. Analysis of hepatic bile in three animals also suggested a more rapid and higher concentration of ^{99}Tc^{m}-PG than ^{99}Tc^{m}-DHT (36% vs. 4% of the injected dose over two hours). Bowel images were not seen in an animal that had undergone excision of the extrahepatic biliary tract, but scans performed after hepaticojejunostomy demonstrated intestinal transit of isotope.

This study shows that the hepatobiliary system can be easily imaged using Technetium-99m labelled compounds which are excreted into bile. These agents may be useful in the diagnosis of obstructive lesions of the extrahepatic biliary tract of adults and infants.

The recent introduction of ^{99}Tc^{m}-labelled compounds which are excreted by liver cells into bile suggests a simple and atraumatic method of investigating the hepatobiliary system (Lin *et al.*, 1974; Eikman *et al.*, 1975; Ronai *et al.*, 1975; Serafini *et al.*, 1975; Van Heertum *et al.*, 1975a). In normal circumstances successive imaging of the liver, gall-bladder and intestine is possible after intravenous injection of a hepatobiliary scanning agent. The advantages of these agents compared with oral cholecystography and intravenous cholangiography includes greater speed and convenience and use in the jaundiced patient. No preparation of the patient is required, and the state of the upper intestinal tract is unimportant, so that the scan may be performed during an acute illness. Furthermore, the presence of radiological contrast material in abdominal organs would not preclude scanning.

The object of this study was to make a preclinical assessment of two Technetium-99m labelled hepatobiliary imaging agents. ^{99}Tc^{m}-dihydrothioctic acid and ^{99}Tc^{m}-pyridoxylidene glutamate were chosen because they can be labelled easily with ^{99}Tc^{m}, an inexpensive isotope with almost ideal physical characteristics for imaging. The experiments have been performed in normal young pigs and in animals that had undergone excisional and reconstructive procedures on the biliary tract. The pig was selected for these studies because its hepatic physiology is similar to the human (Opolon *et al.*, 1971).

MATERIALS AND METHODS

1. A total of 17 scans were performed on ten piglets weighing between 3 and 35 kg. Fourteen of these scans were performed on seven normal animals (eight with ^{99}Tc^{m}-DHT and six with ^{99}Tc^{m}-PG). In order to assess the reproducibility of this technique, five animals underwent one or two repeat examinations with the same agent. A scan was carried out in an animal with obstructive jaundice produced by excision of the gall-bladder and bile ducts (^{99}Tc^{m}-DHT), and also in two animals that had undergone reanastomosis of the bile-duct remnant (^{99}Tc^{m}-DHT).

^{99}Tc^{m}-DHT was prepared from a kit according to the manufacturer's instructions (3-M Company) and the labelling efficiency was assessed by ascending thin layer chromatography using silica gel thin layer chromatographic sheets (Eastman Company). Free pertechnetate (^{99}TcO$_4$-) was determined using acetone as the developing solvent, and the labelled DHT was determined using an ethanol: ammonium hydroxide: distilled water mixture in the ratio of 95:17:16 (v/v) as the developing solvent. In five instances the percentage of free pertechnetate was measured using a well-type scintillation counter and in the remainder labelling efficiency was assessed by visual inspection of the radiochromatograms (Packard 7201 radiochromatogram scanner). ^{99}Tc^{m}-PG was prepared and analysed according to Baker *et al.* (1975). The activity of ^{99}Tc^{m} given for these experiments was 100–300 μCi/kg. The animals were sedated with a combination of Azaperone 0.1 mg/kg (Janssen Pharmaceutica) and Metomidate 0.06 mg/kg (Janssen Pharmaceutica).

Scanning was commenced between four and 20 minutes after injection and was continued for up to two hours with a Nuclear Enterprises Mark IV gamma-camera with a low energy 4000-hole collimator. External ^{57}Co markers were placed over the xiphoid, umbilicus and edge of the right costal margin to facilitate positioning of the liver in the

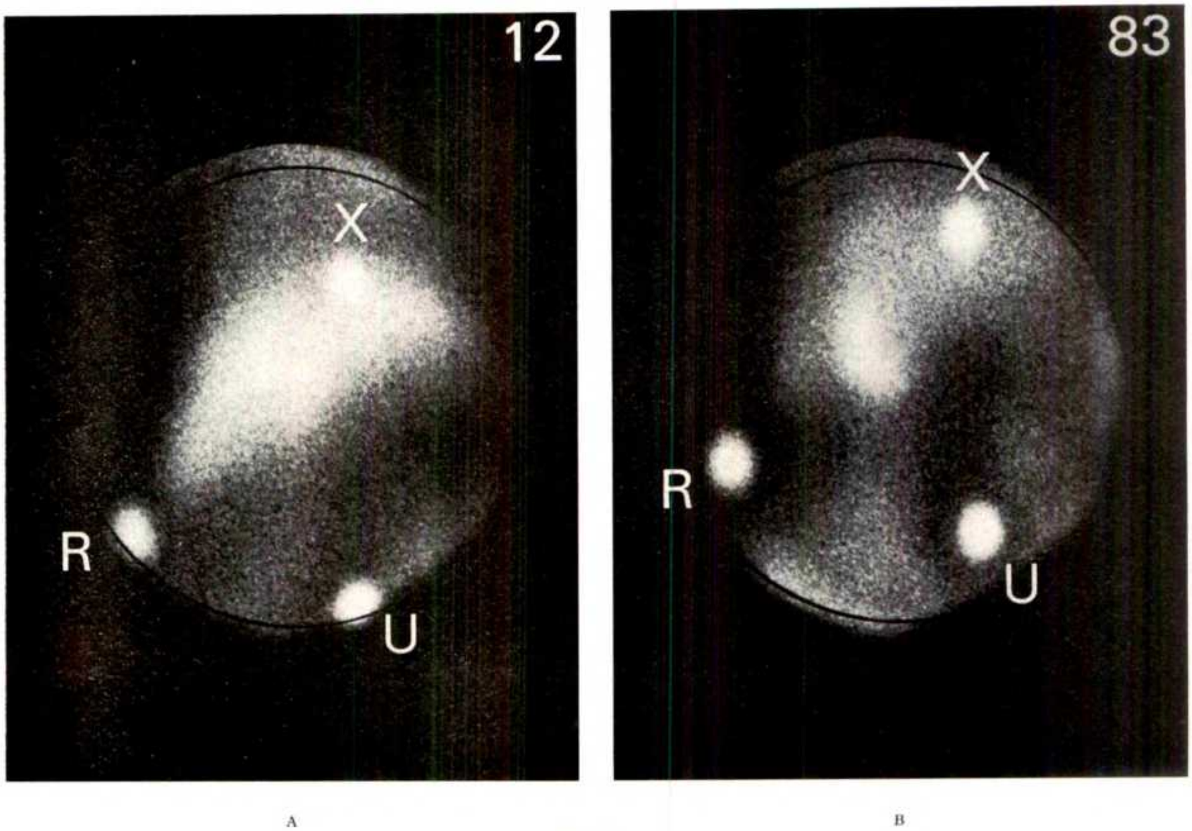

Fig. 1.

(A) ^{99}Tc^m-DHT scan in a normal piglet in the anterior position showing the liver. The number (12) indicates the time after injection of isotope in minutes. The position of external Cobalt markers over the xiphoid, umbilicus, and lateral extremity of the right costal margin is indicated by X, U and R respectively in all figures.

(B) Same scan 71 minutes later. The liver image is faint, and the gall-bladder is now seen between the xiphoid and lateral edge of the right costal margin. Isotope in the intestine is mainly seen between and below the umbilical and right costal margin marker.

field of view of the camera detector. Anterior and right lateral views were obtained. Serial images were recorded on Polaroid film containing 400×10^3 counts. Synthetic octapeptide of Cholecystokinin OP-CCK (Squibb) 40–100 nanograms/kg was injected intravenously into three normal animals to empty the gall-bladder after a definite gall-bladder image had been obtained. This effect in one animal was quantitated by recording the data over the gall-bladder area on videotape and replaying it into a multichannel scaler.

2. Four experiments (two ^{99}Tc^m-DHT and two ^{99}Tc^m-PG) were performed on three anaesthetized pigs (20–35 kg) to determine the time course and concentration with which ^{99}Tc^m-DHT and ^{99}Tc^m-PG was excreted into hepatic bile. One animal received both ^{99}Tc^m-DHT and ^{99}Tc^m-PG. The cystic duct was ligated and the common bile-duct cannulated and ligated around the cannula, so that all hepatic bile was continuously collected. The urinary bladder was catheterized and an intravenous infusion of 5% Dextrose commenced. The radiopharmaceuticals were prepared in the same way as for the scanning procedures. Bile and urine were collected for two hours following injection of the isotope and the amount of radioactivity in these was assayed using a sodium iodine-well scintillation counter.

Results

1. *Hepatobiliary scans*

(a) *Dihydrothioctic acid.* The labelling efficiency for ^{99}Tc^m-DHT was satisfactory as judged by the appearance of the radiochromatograms and gave an average of 3.8% free pertechnetate in five preparations measured with a scintillation detector. Good quality liver images were obtained in the investigations using ^{99}Tc^m-DHT. The liver image appeared between 10 and 15 minutes after injection (Fig 1A).

The image at this stage was comparable with $^{99}\mathrm{Tc^m}$-sulphur colloid images recorded from patients on the same gamma-camera. Consistent hepatobiliary imaging was obtained in all animals that had repeat examinations. The gall-bladder image appeared usually between 30 and 40 minutes after injection and was best seen between 60 and 90 minutes (Fig. 1B). The gall-bladder was imaged satisfactorily in all tests, and we adduced evidence for the presence of a separate gall-bladder image in these experiments from:

(i) the use of radioactive surface markers placed over the xiphoid, umbilicus, right costal margin and lumbar spine;
(ii) imaging in the anterior and right lateral positions;
(iii) the timing and fairly constant appearance of the gall-bladder image:
(iv) a reduction in the number of counts from the gall-bladder area after intravenous OP-CCK;
(v) post-mortem dissection to confirm the normal arrangement of the biliary tract in all animals.

The bile duct, however, was not seen in any scan. In a piglet whose bile ducts had been excised, a faint liver image and no intestinal image was seen (Fig. 2). Two piglets were scanned after reanastomosis of the bile duct had been performed for obstructive jaundice and in both animals a faint liver image and a small intestinal image were obtained (Fig. 3).

(b) *Pyridoxylidene glutamate*. The free pertechnetate averaged $< 1\%$ when tested in four out of the six $^{99}\mathrm{Tc^m}$-PG preparations. A uniform liver image was only briefly obtained with $^{99}\mathrm{Tc^m}$-PG, due possibly to the very rapid excretion of isotope into the biliary system, which was the most striking feature of these scans. The gall-bladder was clearly seen 15 minutes after injection in one animal (Fig. 4) and in another scan the common bile-duct was visualized before the gall-bladder, nine minutes after injection (Figs. 5A, B). In the six scans performed on three animals using $^{99}\mathrm{Tc^m}$-PG the gall-

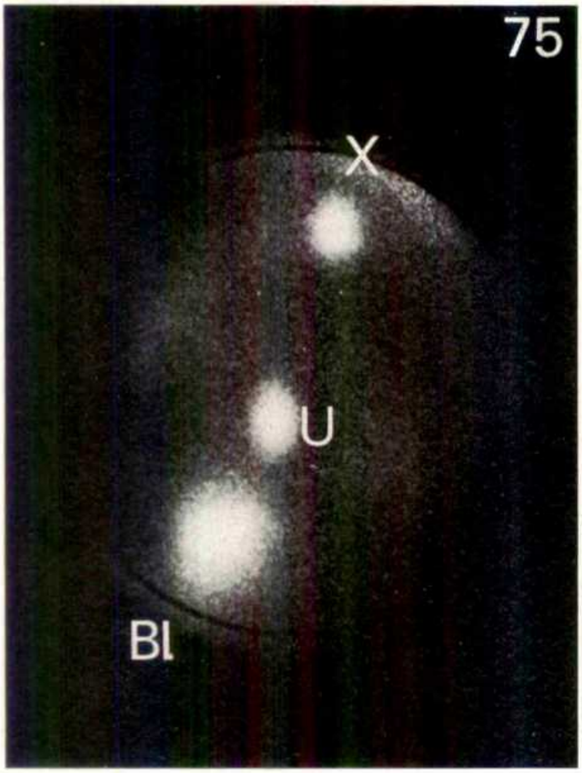

FIG. 2.

$^{99}\mathrm{Tc^m}$-DHT scan of a 6 kg piglet which had undergone excision of the extrahepatic biliary tree five and a half weeks previously. Although a faint liver image was obtained at 50 minutes no gut image was apparent. The urinary bladder is the only organ demonstrated here.

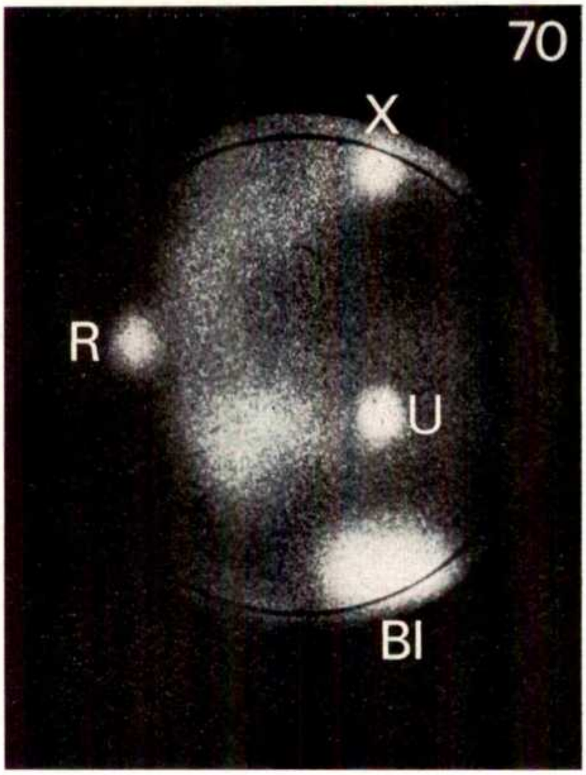

FIG. 3.

$^{99}\mathrm{Tc^m}$-DHT scan carried out after hepaticojejunostomy. A faint liver image is seen. Intestinal isotope is seen in the right lower quadrant of the abdomen, between the bladder, and umbilical and right costal margin markers.

bladder image was evident within 35 minutes of injection. The bile-duct was visualized in one pig weighing 30 kg, but was not identified in either of the scans performed on the two smaller pigs (5 and 8 kg).

The response to intravenous OP-CCK as determined by viewing the Polaroid film images in three piglets was not obvious. There was an apparent slight diminution in size of the gall-bladder image ten minutes after injection of OP-CCK and following a second injection the gall-bladder image was again only slightly altered. However, when the time-activity curve was plotted for the gall-bladder area in one animal the response to the second injection of OP-CCK was marked by a sharp reduction in the number of counts (Fig. 6). This suggests a greater degree of gall-bladder contraction with the larger dose, and also that this method is a sensitive technique for measuring gall-bladder emptying (Dugal *et al.*, 1972).

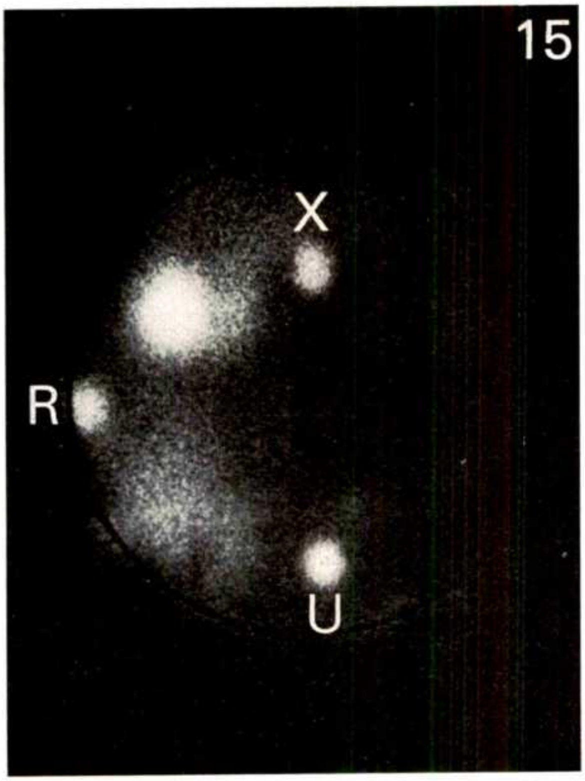

FIG. 4.

^{99}Tc^m-PG scan in a normal piglet (18 kg). The gall-bladder image is more intense than that of ^{99}Tc^m-DHT (Fig. 1A) even in this early picture. Some intestinal excretion of isotope has already taken place (between U and R). There is no liver image.

2. *Excretion of radioactivity in hepatic bile after administration of ^{99}Tc^m-DHT and ^{99}Tc^m-PG*

An average of 4% of the injected dose of ^{99}Tc^m-DHT and 36% of the ^{99}Tc^m-PG were recovered from hepatic bile over the two hours following injection. In the animal where both ^{99}Tc^m-DHT and ^{99}Tc^m-PG were injected on separate occasions the two-hour biliary excretion was 4% and 40% respectively. In the ^{99}Tc^m-DHT experiments maximum radioactivity was obtained in the 40–50 minute bile sample, whereas the peak count for ^{99}Tc^m-PG occurred in the 10–20 minute sample of bile. Analysis of the injected material showed an average of 2.3% free pertechnetate in the ^{99}Tc^m-DHT experiments, and an average of 1.5% free pertechnetate in the ^{99}Tc^m-PG experiments. The amount of radioactivity excreted in the urine over two hours was 19% and 25% for ^{99}Tc^m-DHT and ^{99}Tc^m-PG respectively. These results are in agreement with Van Heertum's data (1975b) for these agents in the conscious baboon, although the difference in biliary excretion between these agents was not as wide in the primate.

DISCUSSION

Hepatobiliary images were easily and consistently obtained with both agents, although the liver image lasted for only a few minutes after injection in the ^{99}Tc^m-PG scan. The time spent in preparation and analysis was approximately 40 minutes for ^{99}Tc^m-DHT and 90 minutes for ^{99}Tc^m-PG. The slower and more persistent liver uptake of ^{99}Tc^m-DHT produced better liver images than ^{99}Tc^m-PG.

The clear and discrete gall-bladder images that were obtained in these experiments may be attributed in part to the relatively superficial position of the gall-bladder. Such clear images with ^{99}Tc^m-DHT may not be possible in man because of the greater volume of liver tissue around the gall-bladder. However, this may be less of a problem with ^{99}Tc^m-PG, as other animal studies suggest higher gall-bladder to liver ratios with ^{99}Tc^m-PG (Baker *et al.*, 1975) than ^{99}Tc^m-DHT (Dugal *et al.*, 1972). The higher percentage of radioactivity detected in the bile after injection of ^{99}Tc^m-PG also suggests that ^{99}Tc^m-PG would be the more suitable agent for determining patency of the extrahepatic biliary tract.

The precise chemical structure and metabolic pathway(s) for ^{99}Tc^m-DHT and ^{99}Tc^m-PG are unknown. The liver appears to be the main organ where these two agents are normally metabolized and excreted, but when liver function is depressed renal clearance of isotope is increased. The different rate and amount of radioactivity that we found in the

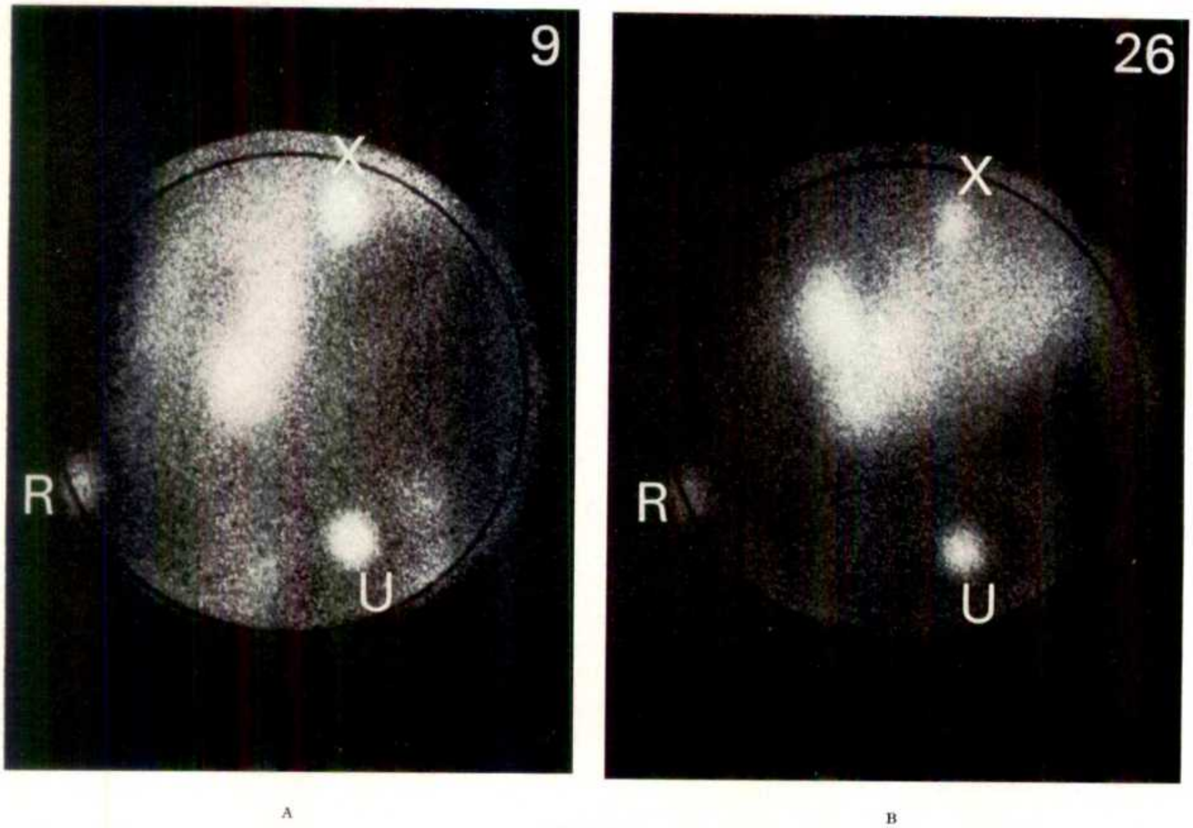

FIG. 5.

(A) Another $^{99}Tc^{m}$-PG scan. On this occasion, the bile duct and duodenum are the first structures to be visualized. Faint renal images on either side of the umbilical marker are also seen in this early picture.

(B) Same $^{99}Tc^{m}$-PG scan 15 minutes later. The gall-bladder is now imaged to the right of the common bile-duct.

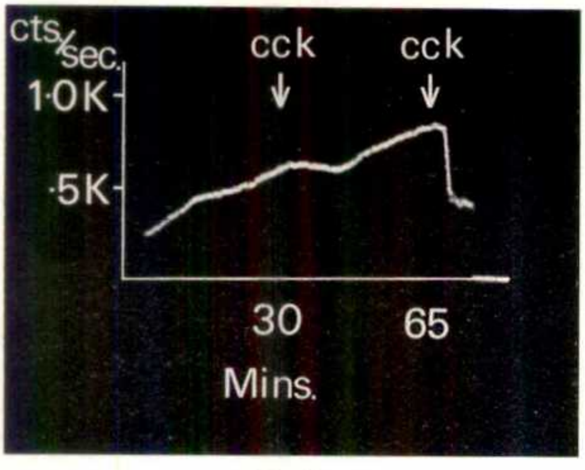

FIG. 6.

$^{99}Tc^{m}$-PG scan. Time-activity curve for the gall-bladder area. Injection of OP-CCK (cck; 100 ng/kg) decreased the count rate indicating normal gall-bladder emptying. A lower dose (60 ng/kg 35 minutes previously) had a slight effect. Vertical axis, kilo counts/second; horizontal axis, time in minutes.

bile of one pig that received both $^{99}Tc^{m}$-DHT and $^{99}Tc^{m}$-PG suggests that the hepatocyte may handle these two agents differently. Mild elevation of bilirubin levels (34–50 μmol/l) due to impaired liver function is a well-known limitation of oral cholecystography and intravenous cholangiography and in the present experiments poor liver images were obtained after injection of $^{99}Tc^{m}$-DHT in three piglets with abnormal liver function. However, in this situation hepatobiliary imaging agents should compare favourably with contrast radiological investigations, because much smaller quantities of radionuclide can be detected in gall-bladder bile by imaging devices than radio-opaque media can by roentgenological means (Eikman *et al.*, 1975).

One might expect hepatobiliary imaging agents to be useful in the diagnosis of acute cholecystitis, because the cystic duct is invariably occluded (Sherlock, 1975). Thus, in a patient with acute upper abdominal pain, the demonstration of a gall-bladder image would suggest that the cause was not acute cholecystitis. Data so far collected in controls and patients with acute cholecystitis has shown good to excellent correlations between hepatobiliary scans and contrast radiological studies (Tonkin and DeLand, 1974; Ronai *et al.*, 1975). Both types of investigation, however, are liable to false-positive errors in normal people (Mujahed *et al.*, 1974; Eikman *et al.*, 1974; Ronai *et al.*, 1975). Eikman *et al.* (1974) were able to reduce this error by first emptying the gall-bladder with intravenous cholecystokinin (75 units). The reason why we did not observe any false-negative gall-bladder images in our normal animals was presumably because they were unstarved. Repeat examination in the same animal produced consistent hepatobiliary images, and suggests that this is a reliable technique. Contrast radiology with its greater resolving power offers more clarity and detail than do isotope scans where gall-stones and polyps would be unlikely to be demonstrated. However, a common bile-duct 10 mm in diameter was easily demonstrated in the present experiments (Fig. 4B).

The excretion of isotope into the bowel may be of value in the diagnosis of obstructive jaundice in infancy where the common differential diagnoses are neonatal hepatitis and biliary atresia. ^{131}Rose Bengal is currently used as a test of biliary tract patency in these infants. However, the test requires the collection of uncontaminated stools over three days and ^{131}I subjects the patient to a higher radiation dose per mCi than ^{99}Tc^{m}. Inasmuch as the piglet is a suitable animal model for paediatric research (Tunell *et al.*, 1972), the present experiments suggest that ^{99}Tc^{m}-PG may provide an alternative diagnostic technique in neonatal obstructive jaundice, for good intestinal imaging has been obtained in animals as small as 3 kg.

In conclusion, the hepatobiliary imaging agents ^{99}Tc^{m}-DHT and ^{99}Tc^{m}-PG have been shown to produce satisfactory liver and gall-bladder images in the healthy piglet and to demonstrate extrahepatic biliary tract patency. It is suggested that hepatobiliary imaging agents may supplement conventional contrast radiological studies in patients with obstructive jaundice and those suspected of having acute cholecystitis. We are evaluating these two agents in adults with obstructive disease of the biliary tract, and, for the reasons stated above, we propose to extend this work to include an assessment of ^{99}Tc^{m}-PG in neonates with prolonged obstructive jaundice.

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Ultrasound in the management of acute pancreatitis*

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Abstract

Thirty-eight patients have been examined by ultrasound when symptoms or signs suggested the development of a pseudocyst following an attack of proven acute pancreatitis. Pseudocyst was diagnosed in 23 of the 38 cases. Five patients had multilocular cysts, four of which were shown to be communicating. Laparotomy was carried out on 14 of the 23 patients and surgical drainage was performed in 12 cases. The remaining nine cases were monitored and showed steady regression. Small cysts arising in the head of pancreas may give rise to recurrent or persistent pancreatitis and may be demonstrated pre-operatively by ultrasound but not readily by other means. A further 12 patients showed an area of irregular absorption of ultrasound interpreted as an inflammatory mass. Monitoring of these cases showed progressive resolution without cyst formation. Three of these cases subsequently required laparotomy—one developed an abscess and one necrosis of the body and tail of pancreas while a third developed severe pancreatic fibrosis of the area identified by ultrasound. The ability to distinguish between pseudocysts and inflammatory masses and to demonstrate communication between multiple cysts is of considerable value in pre-operative diagnosis.

Ultrasound scanning of the pancreas has been used in the investigation of pancreatic pseudocysts for several years (Filly and Freimanis, 1970; Holm, 1971; Leopold, 1972). The value of ultrasound in determining therapy by differentiating between pancreatic pseudocysts and inflammatory masses by the A-scan technique has been referred to only more recently (Bradley and Clements, 1974). It is of interest to note that even in recent series of pancreatic pseudocysts in the surgical literature (Sankaran and Walt, 1975; Hollender *et al.*, 1975), only passing reference is made to the possible value of ultrasound in diagnosis. Folk and Freeark (1970) refer to a case found at surgery to have pancreatic and peripancreatic oedema simulating pseudocyst. Barium-meal examination is the conventional and most widely used method of diagnosis in suspected pancreatic pseudocysts. However, the investigation fails to diagnose as many as 25% of pseudocysts (Sankaran and Walt, 1975); this is particularly so in small cysts of the head of the pancreas.

The purpose of this paper is to evaluate the role of ultrasound in the diagnosis of upper abdominal masses following acute pancreatitis.

Material and Methods

Over the past three and a half years a group of 38 patients has been referred for ultrasound examination following a proven attack of acute pancreatitis when signs or symptoms suggested the development of a pancreatic pseudocyst. Two cases followed blunt trauma to the abdomen.

Prior to the ultrasound examination, all patients had a plain film of the abdomen with a marker placed on the umbilicus so that the presence and site of bowel gas could be identified. All cases were examined in the supine position using the compound B-scan direct contact technique (Duncan, 1975). The abdomen was examined at appropriate levels in transverse and longitudinal planes and the scans were recorded on Polaroid film using the Nuclear Enterprises Diasonograph NE 4101 with transducers of 1.5 and 2.5 MHz.

Results

The patients have been classified according to the ultrasound findings and those confirmed or not confirmed at laparotomy are recorded. Also recorded are those undergoing spontaneous resolution and the results are shown in Table I. The pseudocyst group is subdivided into three categories—single cysts, multiple cysts and small cysts arising in the head of the pancreas. These are recorded in Table II.

Pseudocysts

An ultrasonic diagnosis of pseudocyst was made in 23 (60%) of 38 patients. Laparotomy was carried out in 14 of the 23 patients. Pseudocyst was confirmed in 13, and in one no cyst was found. Pseudocysts are transonic and are typically circular or elliptical with a clearly defined margin extending around the circumference of the cyst, particularly posteriorly. Structures deep to the cyst, *e.g.* kidneys, vertebral column, aorta, vena cava, are clearly demonstrated indicating its transonic nature. A typical example is shown in Fig. 1.

Despite their retroperitoneal position, pseudocysts arising from the body or head of pancreas may extend forwards to the anterior abdominal wall and give the appearance of an anterior abdominal cyst.

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*Based on a paper read at the British Medical Ultrasonics Group Meeting, Bristol, December 16, 1975.

TABLE I

THIRTY-EIGHT CASES OF CLINICALLY SUSPECTED PSEUDOCYST

Ultrasound Diagnosis	No. of patients	Surgical resection or drainage	Confirmed at operation	Not confirmed at operation	Spontaneous resolution
Cysts	23	14	13	1	9
Inflammatory masses	12	3	3	—	9
Negative	3	0	—	—	—

TABLE II

TWENTY-THREE CASES OF PSEUDOCYSTS

Cysts	No. of patients	Confirmed at operation	Not confirmed at operation	Spontaneous resolution
Single	15	7	—	8
Multiple	5	4	—	1
Small—pancreatic head	3	2	1	—
Total	23	13	1	9

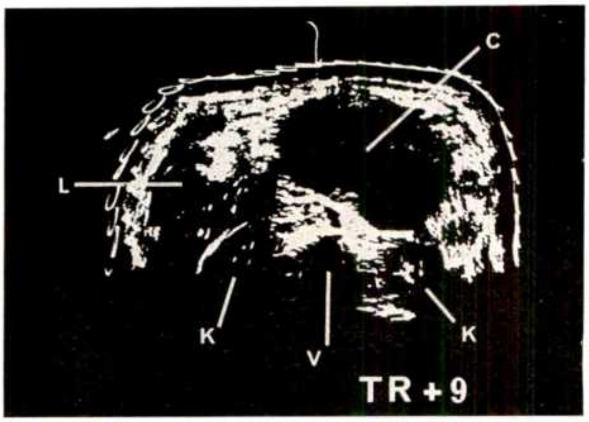

FIG. 1.

Pancreatic pseudocyst showing clearly defined margin and posterior structures. C = pseudocyst; L = liver; K = kidney; V = vertebra; TR = transverse scan above the plane of the umbilicus measured in centimetres.

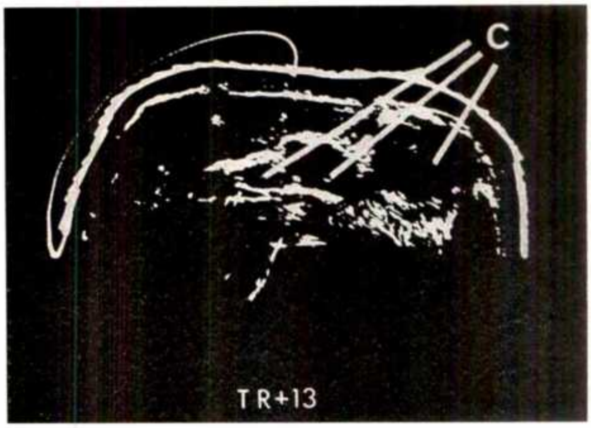

FIG. 2.

Multilocular pancreatic pseudocyst showing communicating loculi. C = Cyst loculi.

This has been noted particularly in cases of pancreatic trauma and both cases of blunt trauma in this series developed large mid-line cysts.

Of the 23 cases, five showed bilocular or multilocular cysts. Communication between loculi was demonstrated by ultrasound in four cases and was subsequently confirmed at laparotomy. A typical case is shown in Fig. 2. Serial scans carried out on a fifth patient showed spontaneous resolution of a cyst in the tail of the pancreas but persistence of an asymptomatic cyst in the head. Two of the above four cases are of particular interest.

Case 1

A 21-year-old male who, on his second admission for acute pancreatitis, developed a left hypochondrial swelling. Ultrasound examination demonstrated a multilocular communicating cyst with an anterior and a retrogastric component (Fig. 3). Following clinical improvement, the abdominal swelling regressed and repeat ultrasound scanning showed that the anterior component of the cyst had resolved but the posterior component had persisted unchanged. After further recurrence of acute pancreatitis, the abdominal swelling recurred and the anterior component was again demonstrated. At laparotomy posterior cystogastrostomy was performed and both cysts decompressed simultaneously, confirming the communication demonstrated on ultrasound.

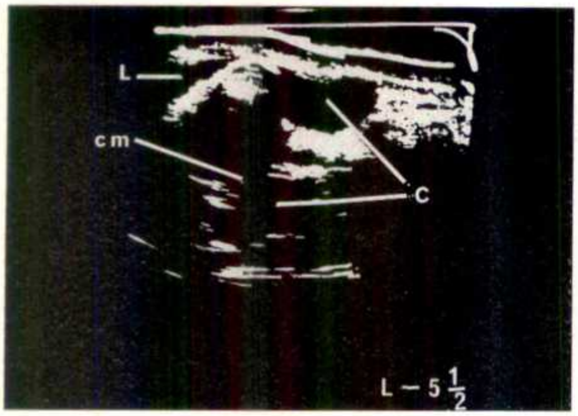

FIG. 3A.

Pancreatic pseudocyst showing anterior and posterior components with intercommunication. C = anterior and posterior components of pseudocyst; cm = communication; L = liver; $L-5\frac{1}{2}$ = longitudinal scan to the left of the midline measured in centimetres.

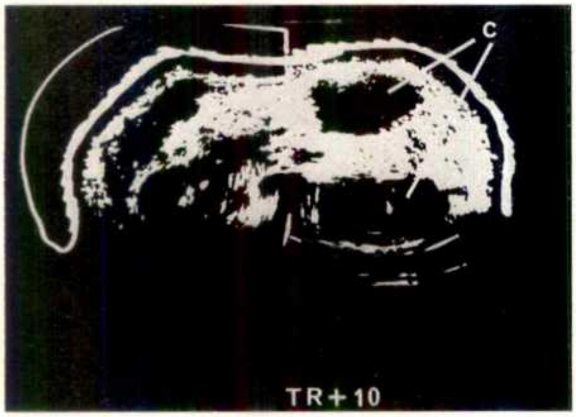

FIG. 3B.

Anterior and posterior components of pancreatic pseudocyst. TR + 10 = transverse scan above the plane of the umbilicus measured in centimetres.

Case 2

A 49-year-old male who was admitted to hospital with severe peri-umbilical abdominal pain. There was a previous history of duodenal ulcer and perforation. Barium meal showed an annular constriction of the second part of the duodenum. At laparotomy a large mass was demonstrated at this site and a gastroenterostomy was performed. Symptoms persisted and a persistently high serum amylase was recorded. Subsequent endoscopy suggested an extra-duodenal mass and an ultrasound scan showed a multilocular cystic structure surrounding the duodenum (Fig. 4). Further laparotomy revealed a multilocular pseudocyst arising in the head of the pancreas and encircling the duodenum. Cyst jejunostomy was carried out with relief of symptoms and resolution was proven subsequently by ultrasound.

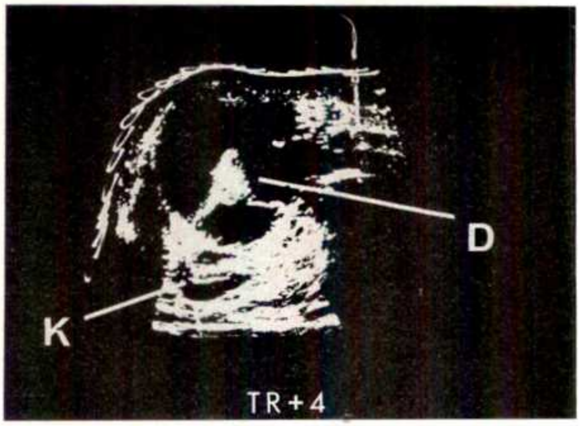

FIG. 4.

Periduodenal loculated pseudocyst showing septa. D = cross section of second part of duodenum; K = right kidney.

Three patients with persisting symptoms of abdominal pain and vomiting were found to have small cysts (less than 6 cm in diameter) in the head of the pancreas. Two were proven at laparotomy and have been successfully treated by surgical drainage while in one patient no definite lesion could be identified.

The remaining nine cases of this group, consisting of eight single cysts and one multiple cyst, were monitored over periods varying from four to 12 weeks and showed spontaneous regression. These patients have now been followed up for a minimum period of six months and are all well. As regression proceeds, cysts may become crenated and difficult to define, particularly when 3 cm or less in diameter.

INFLAMMATORY MASSES

In 12 of the 38 cases, the ultrasonic appearances were quite different from pseudocyst. Absorption of ultrasound occurred over the pancreatic area or site of the abdominal swelling so that posterior structures could not be identified and the margin of the area was poorly defined (Fig. 5). The presence of bowel gas as a cause of absorption was excluded by reference to the plain film of abdomen. In some instances, the palpable abdominal swelling could be readily correlated with the area of ultrasound absorption. This appearance has been interpreted as representing a pancreatic inflammatory mass.

Serial scanning of these 12 patients showed resolution of the mass over periods varying from 4 to 20 weeks. None of these cases developed a pseudocyst but three have required operation subsequently. One has developed an abscess and one necrosis of

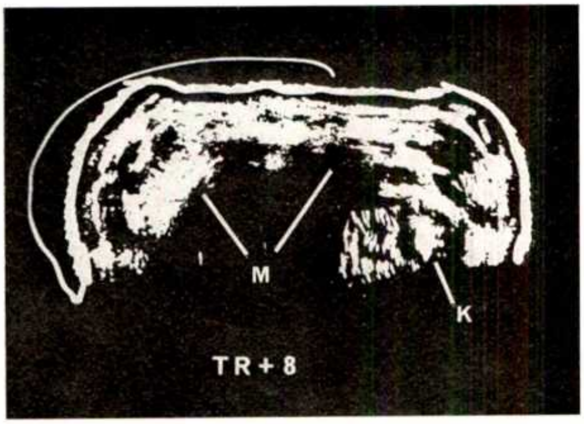

Fig. 5.

Pancreatic inflammatory mass showing absence of posterior abdominal structures due to absorption of ultrasound. M = inflammatory mass; K = left kidney.

the body and tail of pancreas while a third developed severe pancreatic fibrosis of the area identified by the ultrasound scan.

Negative Findings

In the remaining three cases who had symptoms and clinical suspicion of an upper abdominal mass, no cyst or inflammatory mass could be demonstrated on ultrasound. All these patients improved spontaneously without surgical intervention.

Aetiology

Alcohol-related acute pancreatitis more frequently resulted in pseudocyst formation than pancreatitis associated with biliary disease. In this series there were 12 cases related to alcohol, six to biliary disease, two to trauma and three to other causes.

Discussion

Prior to the introduction of ultrasound techniques, patients suspected of developing a pancreatic pseudocyst following acute pancreatitis or pancreatic trauma have been investigated by barium-meal studies. In a series of 112 cases of pancreatic pseudocyst, barium meal demonstrated a mass in the region of the pancreas in only 75% of cases (Sankaran and Walt, 1975). Deformity and displacement of the upper gastrointestinal tract may demonstrate the site of a mass but not its nature. Nevertheless, in a high proportion of such cases, a diagnosis of pancreatic pseudocyst will be made. How frequently this diagnosis is correct is difficult to determine as most studies report only surgically-proven cases of pseudocyst. Few authors have recorded how frequently they have failed to find a pseudocyst at laparotomy when symptoms and signs have been suggestive of pseudocyst formation.

Although cystic structures lend themselves particularly to detection by ultrasound, it is of interest to note that, even in recent series of pancreatic pseudocysts, only passing reference is made to the possible value of ultrasound in diagnosis (Sankaran and Walt, 1975; Hollender *et al.*, 1975).

Ultrasound has added a new dimension to the investigation of acute pancreatitis and its sequelae. Attention has been drawn to the use of ultrasound in differentiating pseudocysts from inflammatory masses of pancreas using the A-scan technique (Bradley and Clements, 1974). In 25 consecutive patients with a clinical diagnosis of pancreatic pseudocyst, these authors found that of 13 showing ultrasound appearances of solid tissue, eight were subsequently proven to have peripancreatic oedema at laparotomy or autopsy.

Of 23 cases of pseudocyst diagnosed by ultrasound in this series, only one was not confirmed at operation. This was a suspected small cyst in the head of pancreas. The remaining nine cases not submitted to operation were monitored at intervals and all regressed spontaneously.

In our experience, the main value of ultrasound is the ability to differentiate between true cystic and inflammatory masses in suspected pseudocyst in the period immediately following acute pancreatitis. Unnecessary laparotomy may thereby be avoided. Timing of surgery is helped by monitoring the size and shape of the pseudocyst and the number of pseudocysts which resolve spontaneously may be ascertained. This is the subject of some controversy in the surgical literature. Regression of pseudocysts in the post-operative period can also be monitored. The ability of this non-invasive method to demonstrate multiple cysts or loculations as well as communication between them is a considerable advance in pre-operative diagnosis. The incidence of multilocular or multiple pseudocysts varies in different series. Sankaran and Walt (1975) report an incidence of 6% whereas Anderson (1972) found 23%. The incidence in this series is 22% and it is of interest to note that alcohol was considered to be the cause of the pancreatitis in all five patients.

The finding of pseudocyst formation more commonly in those with alcohol-associated pancreatitis is noteworthy as our own prospective studies of acute pancreatitis (Imrie and Whyte, 1975; Imrie and Blumgart, 1976) show an overall incidence of biliary disease at least twice that of alcohol-induced pancreatitis. This indicates that pancreatic-duct disruption leading to pseudocyst development is probably more likely to occur in alcohol-associated disease.

Small cysts persisting in the head of the pancreas may cause severe continuing symptoms of pancreatitis and give rise to difficult clinical problems (Sankaran and Walt, 1975). Detection of these small cysts may not be possible by palpation or barium studies prior to laparotomy (Nardi *et al.*, 1969). In our experience, it would seem that ultrasound is of value in detecting such cases, two of three suspected cases being subsequently proven at laparotomy.

Filly and Freimanis (1970) describes a transonic arc-shaped plate anterior to the aorta which they have noted in acute pancreatitis and which they consider to be characteristic of pancreatic oedema. Several of our cases were scanned in the acute phase of pancreatitis but we have been unable to demonstrate this appearance.

Bradley and Clements (1974) seem to be the first to have drawn attention to the significant incidence of solid masses in cases of suspected pseudocyst. Of our 12 patients diagnosed as an inflammatory mass, nine resolved completely and three required exploration because of abscess formation, pancreatic necrosis or fibrosis but none developed a pseudocyst. These three patients developed complications consistent with a previous pancreatic inflammatory mass, thus supporting the original ultrasound diagnosis. Ultrasonic scanning can provide useful information in the management of acute pancreatitis not obtainable by other non-invasive means.

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Book review

Basic Anatomy and Physiology for Radiographers. 2nd Edition. By M. R. E. Dean, pp. 413, 1975 (Oxford, Blackwell Scientific Publications), £6·75.

The second edition of this book has come five years after the first. It has almost 30 extra diagrams to clarify the text, and some of the chapters are updated and rewritten.

Three of the extra diagrams come in the chapter on "Surface and Regional Anatomy" and illustrate the mediastinum, and the relationships of its vessels. These are useful, especially now that knowledge of topographical anatomy plays an increasing part in the student radiographer's life.

An example of updating comes in "General Pathology", where ethlyene oxide is included as a sterilising agent. "The Circulatory System" has been rewritten and rationalized in parts; for instance, pulmonary and systemic circulations have been distinguished, and there are some diagrams added in this chapter too.

The greatest alteration appears in the chapters on muscles and joints, which have been combined into one extended chapter, and the function and involvement of the various muscles during movement is ably yet simply demonstrated.

In my opinion, this book will prove even more useful than its earlier edition, and will be a popular basic text for the D.S.R. course.

ELIZABETH C. SALMON.

1976, *British Journal of Radiology*, *49*, 863–867 OCTOBER 1976

A computer-based radiotherapy clinical record system using mark-sense forms

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ABSTRACT

A computer-based system for radiotherapy clinical records is described. Its main features are the use of a single mark-sense form for input of data at all stages of the patient's progress, and the provision of a plain language print-out of the patient's record after each updating. The programs are written in Fortran and are implemented on a Rank Xerox Sigma 6 computer.

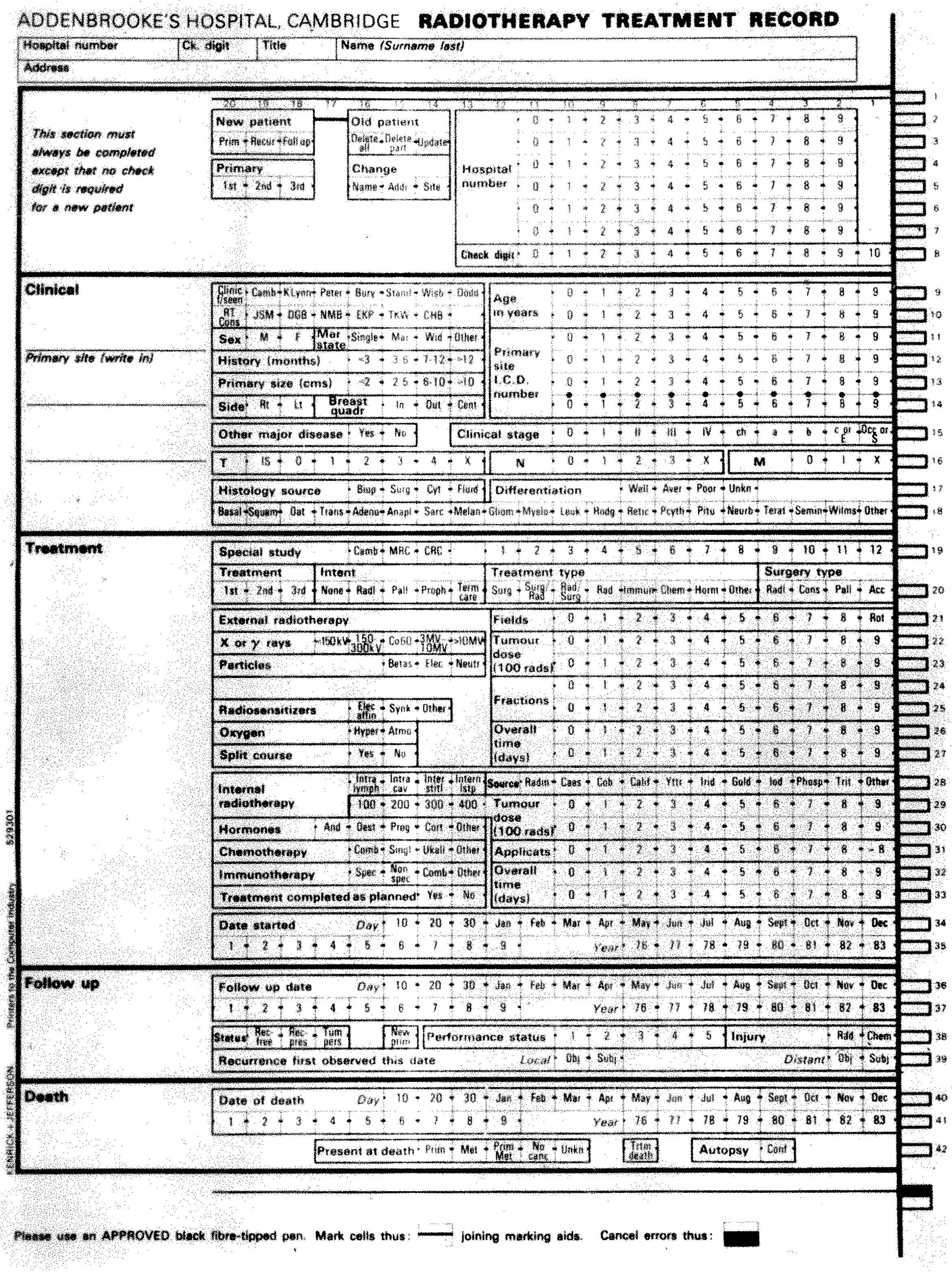
The Joint Working Party of the Faculty of Radiologists and The British Institute of Radiology in their report (1969) noted that there were two aspects of the data available on radiotherapy patients that were of special interest: (1) the provision of statistics for the National Cancer Registration Scheme and (2) the collection of clinical and radiotherapeutic details for the individual Centre or the Regional Cancer Registry.

The Joint Working Party also produced a Minimal List of Variates which it considered "would be necessary for each patient to allow the most basic analysis". While containing items all of which are no doubt desirable to record, this list is of formidable length and would require considerable clerical effort both to record in the first place and then to translate into a medium suitable for input to a computer.

In considering the introduction of a computer-based radiotherapy patient record in this Centre, we were concerned that it could be put into operation with only a small amount of extra staff effort, and also that there should be a minimum likelihood of errors (*e.g.* due to miscoding) creeping in during the preparation of computer input from the clinician's initial notes. This led us to the choice of a mark-sense document, which could be completed rapidly by the clinician himself as the means of recording the data. Such a document has already been used for recording patient data in other specialties (Bennett and Holland, 1965). The mark-sense form (described in detail below and shown in Fig. 1) has on it a series of boxes, in each of which a piece of information can be recorded by drawing a line across the centre of the box with a black fibre-tipped pen. The boxes can be labelled in ordinary language, thus largely avoiding the need for numerical codes and the availability of a coding book close to hand when completing the form. After completion, the mark-sense forms can be passed through a special document reader which translates the marks into characters punched out on a paper tape, and this tape can then be used to transfer to a computer the information that was on the form. An alternative approach used by Bruce *et al.* (1970) is to type information in plain language on cards which can be read by an optical character recognition reader, but this still has the disadvantage of interposing a clerk or typist between the clinician and the computer.

We further decided that, to simplify procedures, one type of mark-sense form should be used for recording all stages of a patient's progress and that the form should be of a size (216 mm × 285 mm) that would easily slip into the folders containing the patient's notes. These constraints obviously limited the amount and type of data recorded to less than the "Minimal List of Variates", but we believe our system includes sufficient to make possible by computer the large majority of analyses that are likely to be required in a radiotherapy department.

Other features aimed at in our system were flexibility of updating and ease of alteration or correction of any part of a patient's record. Information can be added to a record at any time just by filling in the new information on a form; thus the creation or prompt updating of a record need not be held up because of the lack of some pieces of information which can be added later when available. To facilitate checking of the information on the file we felt that a plain language print-out of the patient record was necessary after each update. This was a feature of the computer based record system for the study of hypertension by Beilin *et al.* (1974), Bulpitt *et al.* (1976) and, when produced in duplicate, provides copies for both the patient's notes in the Radiotherapeutic Centre and also for those in the referring hospital.



ADDENBROOKE'S HOSPITAL, CAMBRIDGE **RADIOTHERAPY TREATMENT RECORD**

Hospital number | **Ck. digit** | **Title** | **Name** *(Surname last)*
Address

20 19 18 17 16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 — 1

This section must always be completed except that no check digit is required for a new patient

New patient — Prim · Recur · Foll up
Old patient — Delete all · Delete part · Update
Primary — 1st · 2nd · 3rd
Change — Name · Addr · Site

Hospital number — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 2
0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 3
0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 4
0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 5
0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 6
0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 7
Check digit — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 · 10 — 8

Clinical

Primary site (write in)

Clinic f/seen — Camb · KLynn · Peter · Bury · Stam · Wisb · Dodd | Age in years — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 9
RT Cons — JSM · DGB · NMB · EKP · TKW · CHB | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 10
Sex — M · F | **Mar state** — Single · Mar · Wid · Other | Primary site I.C.D. number — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 11
History (months) — <3 · 3-6 · 7-12 · >12 | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 12
Primary size (cms) — <2 · 2-5 · 6-10 · >10 | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 13
Side — Rt · Lt | **Breast quadr** — In · Out · Cent | ·0 · ·1 · ·2 · ·3 · ·4 · ·5 · ·6 · ·7 · ·8 · ·9 — 14
Other major disease — Yes · No | Clinical stage — 0 · I · II · III · IV · ch · a · b · c or E · Occ or S — 15
T — IS · 0 · 1 · 2 · 3 · 4 · X | **N** — 0 · 1 · 2 · 3 · X | **M** — 0 · 1 · X — 16
Histology source — Biop · Surg · Cyt · Fluid | **Differentiation** — Well · Aver · Poor · Unkn — 17
Basal · Squam · Oat · Trans · Adeno · Anapl · Sarc · Melan · Gliom · Myelo · Leuk · Hodg · Retic · Pcyth · Pitu · Neurb · Terat · Semin · Wilms · Other — 18

Treatment

Special study — Camb · MRC · CRC | 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 · 10 · 11 · 12 — 19
Treatment — 1st · 2nd · 3rd | **Intent** — None · Radl · Pall · Proph · Term care | **Treatment type** — Surg · Surg/Rad · Rad/Surg · Rad · Immun · Chem · Horm · Other | **Surgery type** — Radl · Cons · Pall · Acc — 20

External radiotherapy | **Fields** — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · Rot — 21
X or γ rays — <150kV · 150-300kV · Co60 · 3MV-10MV · >10MV | **Tumour dose (100 rads)** — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 22
Particles — Betas · Elec · Neutr | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 23
Fractions — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 24
Radiosensitizers — Elec affin · Synk · Other | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 25
Oxygen — Hyper · Atmo | **Overall time (days)** — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 26
Split course — Yes · No | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 27

Internal radiotherapy — Intra lymph · Intra cav · Inter stitl · Intern istp | **Source** — Radm · Caes · Cob · Calif · Yttr · Irid · Gold · Iod · Phosp · Trit · Other — 28
100 · 200 · 300 · 400 | **Tumour dose (100 rads)** — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 29
Hormones — And · Oest · Prog · Cort · Other | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 30
Chemotherapy — Comb · Singl · Ukali · Other | **Applicats** — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · - 8 — 31
Immunotherapy — Spec · Non spec · Comb · Other | **Overall time (days)** — 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 32
Treatment completed as planned — Yes · No | 0 · 1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 — 33

Date started *Day* — 10 · 20 · 30 · Jan · Feb · Mar · Apr · May · Jun · Jul · Aug · Sept · Oct · Nov · Dec — 34
1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 | *Year* — 76 · 77 · 78 · 79 · 80 · 81 · 82 · 83 — 35

Follow up

Follow up date *Day* — 10 · 20 · 30 · Jan · Feb · Mar · Apr · May · Jun · Jul · Aug · Sept · Oct · Nov · Dec — 36
1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 | *Year* — 76 · 77 · 78 · 79 · 80 · 81 · 82 · 83 — 37
Status — Rec-free · Rec-pres · Tum pers | New prim | **Performance status** — 1 · 2 · 3 · 4 · 5 | **Injury** — Rdd · Chem — 38
Recurrence first observed this date *Local* — Obj · Subj | *Distant* — Obj · Subj — 39

Death

Date of death *Day* — 10 · 20 · 30 · Jan · Feb · Mar · Apr · May · Jun · Jul · Aug · Sept · Oct · Nov · Dec — 40
1 · 2 · 3 · 4 · 5 · 6 · 7 · 8 · 9 | *Year* — 76 · 77 · 78 · 79 · 80 · 81 · 82 · 83 — 41
Present at death — Prim · Met · Prim Met · No canc · Unkn | Trtm death | **Autopsy** — Conf — 42

Please use an APPROVED black fibre-tipped pen. Mark cells thus: —— joining marking aids. Cancel errors thus: ■

KENRICK + JEFFERSON Printers to the Computer Industry 529301

FIG. 1.
The mark-sense form.

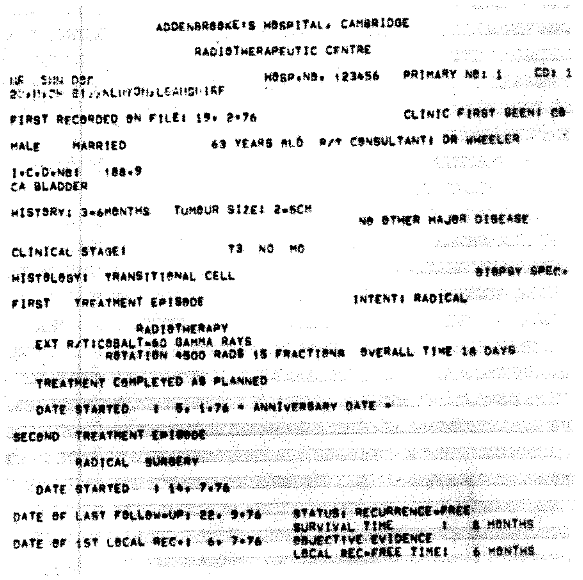
DESCRIPTION OF SYSTEM

All the information is entered by marks on a mark-sense form, except for the patient's name, address and a description in words of the primary site or diagnosis. This literal data normally has to be entered only once when the patient record is first created on the file and, at that time, is punched on paper tape using a Teletype key board. The mark-sense forms are read by a Dataterm 3 Terminal Document Reader (Data Recognition, Ltd.), which produces its output also on paper tape. Thus, when a batch of forms is being processed by the system, there are two input paper tapes, one containing the information on all the forms and the other containing the literal data for any new patients, and also (as explained below) for any changes in name, address or site that need to be made on an existing record.

Two programs, written in Fortran, and running on a Rank Xerox Sigma 6 computer, handle this input. The first deduces the patient number from the mark-sense form information, calculates the check digit and, if it is for an old patient, checks that this calculated check digit corresponds to that marked on the form. The check digit is calculated from the digits of the patient's number and, although not unique to one patient number, is nearly always altered by transposition and other types of errors that are common in entering numbers. We have found in practice that this procedure provides an adequate safeguard against entering information on a wrong patient number. The program also checks for other inconsistencies or errors in the completion of the first part of the form. If all these checks are satisfactory, then the program merges the literal data with its corresponding mark-sense data to produce fixed length records 364 characters long, headed by the patient number.

The second program uses these records (after being sorted into ascending order of patient number) as input, and also the up-to-date version of the patient file. The latter consists of patient records, each 444 characters long headed by the patient number, and also arranged in ascending order of patient number. New patient records are slotted in at the appropriate point; update information is merged with existing records. In this process any update information in a particular category overwrites any existing information in that category. This provides a simple method of correcting records. For example, if the marital state on the record of a married person has previously been recorded wrongly as single, a subsequent update form with a mark in the married box will correct the error.

Output from the second program is the new updated file of patient records and also a print-out in plain language of the information held on each of the patients for whom a form has been processed in the current run (Fig. 2).



```
                    ADDENBROOKE'S HOSPITAL, CAMBRIDGE

                       RADIOTHERAPEUTIC CENTRE

MR  SMN DOE                          HOSP.NO. 123456   PRIMARY NO: 1    CD: 1
2[illegible]

FIRST RECORDED ON FILE: 15. 2.76                       CLINIC FIRST SEEN: CB

MALE    MARRIED             63 YEARS OLD  R/T CONSULTANT: DR WHEELER

I.C.D.NO:   188.9
CA BLADDER

HISTORY: 3-6MONTHS   TUMOUR SIZE: 2-5CM
                                              NO OTHER MAJOR DISEASE

CLINICAL STAGE:             T3  NO  MO

HISTOLOGY:  TRANSITIONAL CELL                              BIOPSY SPEC.

FIRST   TREATMENT EPISODE                     INTENT: RADICAL

              RADIOTHERAPY
   EXT R/T:COBALT-60 GAMMA RAYS
           ROTATION 4500 RADS 15 FRACTIONS  OVERALL TIME 18 DAYS

   TREATMENT COMPLETED AS PLANNED

   DATE STARTED   :  5. 1.76 * ANNIVERSARY DATE *

SECOND  TREATMENT EPISODE

         RADICAL  SURGERY

   DATE STARTED   : 14. 7.76

DATE OF LAST FOLLOW-UP: 22. 9.76    STATUS: RECURRENCE-FREE
                                    SURVIVAL TIME      :   8 MONTHS
DATE OF 1ST LOCAL REC.:  6. 7.76    OBJECTIVE EVIDENCE
                                    LOCAL REC-FREE TIME:   6 MONTHS
```

FIG. 2.

Example of the plain language print-out of a patient's record that is provided after each updating.

THE MARK SENSE FORM

Edwards (1972), in reviewing the need for computing radiotherapy records, drew attention to the four main sections of a record namely: (1) Identification of the patient, (2) Diagnosis, (3) Treatment, and (4) Follow-up. The layout of our form follows this same pattern.

Identification of the patient

When the patient is first seen and a clinical record started for the Radiotherapeutic Centre, the patient's hospital number, name, title and address are written in handwriting in the spaces provided at the top of the form. After this initial entry, only the name is written on the sheet for ease of recognition by the clinician, all other information being recorded by marking the appropriate boxes. Errors noted while the form is being completed can be cancelled by completely blacking in the lower half of the box.

The first part of the form relates to identity. The top left hand section allows a distinction to be made between new patients referred for treatment of a primary tumour, and those referred for treatment of recurrence or for follow-up after primary treatment elsewhere. Provision is also made for creating further records if a patient has a second or third primary tumour. The adjacent block of boxes enables possible options on an already existing record to be chosen. The form may just contain information for updating the record, or it may also be necessary to alter details of the name, address or site. In this case the correct literal data is written in the appropriate spaces on the form, so that it can be punched on paper tape as mentioned above.

Another useful facility is to be able to delete a whole patient's record if for any reason it becomes corrupted, or to delete a part that is in error which cannot be deleted by over-writing as described earlier. In the latter case, after completing this section of the form, marks are only made in the remaining part of the form on information that requires deletion. The right hand boxes in this section enable the hospital number and check digit to be entered.

Diagnosis and clinical record

The clinical record is shown in detail in the next part of the form. Most of the box labels need no further explanation. The I.C.D. number is the one numerical code used in completing the form. The clinician writes in the primary site and diagnosis on the left hand side of the form, and the I.C.D. number boxes are completed by a clerical assistant using the Classification of Anatomical Sites published by the Office of Population Censuses and Surveys (1974).

The form accommodates all the methods of staging currently in use in the Radiotherapeutic Centre. These include the TNM classification of the U.I.C.C. (1974) (excluding a, b and c sub-groups), and a local modification of the staging of lymphomas recommended by Peters *et al.* (1966). Provision is also made for the requirements of the Annual Report on the results of treatment in carcinoma of the uterus, vagina and ovary (Kottmeier, 1973).

The histological subdivisions were chosen by the authors to reflect their clinical practice and interests.

Treatment

The next part of the form is used to record details of treatment. The first row of boxes allows for ready retrieval of patients entered into a clinical trial or special study. Details of up to three courses of treatment can be stored on the computer record. The overall intent and the intent of any surgery are recorded separately.

Details of radiotherapy, use of sensitizers, tumour dose, fractions, overall time and split courses need no further explanation. Space is provided for recording both external and internal radiotherapy. In the latter case, radiation dose can be entered up to a maximum of 40 000 rad. The information on hormones, cytotoxic chemotherapy and immunotherapy is necessarily limited because of the number of variables in the constituents of a régime. The details of dosage and whether or not attention has been paid to cell kinetics are essential in chemotherapeutic practice, but are beyond the scope of this form. Failure to complete the treatment as planned can be noted, and the section ends with the date on which treatment was begun. The patient's anniversary date is the date when the first treatment episode was started.

Follow-up

The follow-up section of the form need not be filled in at every attendance of the patient, but can be completed as frequently as is considered necessary to keep the computer record up to date. When a recurrence occurs, the date of the follow-up when this was first reported is recorded on the computer record together with information on whether the recurrence was local or distant and also whether the evidence for its existence was subjective or objective. Treatment of recurrence can then be recorded in the Treatment section as a second (or third) course of treatment. The presence of radiation- or chemotherapy-induced morbidity can also be noted.

Death

The last part of the form is used to record the date of death, the state of the disease at the time of death and whether the latter was based on autopsy findings. A separate box is also provided to be marked if death is directly attributable to treatment.

CLINICAL USE

The system was introduced in the authors' clinics on 1.1.74 and over 1300 patients were recorded on the file in the first two years. Whenever a new patient was seen in a clinic the first part of the form and the clinical details were filled in, thus ensuring that the patient was entered on the computer file. The only data necessary to complete these two parts of the form are the patient's notes and details of the staging procedures which the clinicians always carried with them.

For in-patients the treatment details were recorded at the time the discharge summary was dictated, when all relevant details were to hand. For out-patients this section of the form was filled in on completion of the treatment. Inevitably a few patients were missed on completion of treatment, but these could be trapped when the computer printout (Fig. 2) appeared in the notes, and details of their treatment could then be completed at their first follow-up appointment.

The form has been found to be simple and rapid to use in practice and has not unduly delayed the progress of clinics. Knowing the relevant details required for the form helped to ensure collection of these details in our case notes. This potential benefit has been noted by other authors (Bulpitt *et al.*, 1976).

In the light of the first year's experience some modifications were made to the original mark-sense form, and the improved version that is in current use is described in this paper. Since the beginning of 1976 other clinicians in the Radiotherapeutic Centre have started to use the system for their patients. A number of programs are available for analysis of the data on file. One of these enables the records of any subgroup of patients having specified characteristics to be either just counted, or written onto a separate file for further analysis, or printed out in the form shown in Fig. 2. A second program will produce standard tables showing the distribution of patients on the file by sex, marital status, site, consultant and referring clinic. Other programs are being written to calculate survival and recurrence-free rates in any required group of patients.

ACKNOWLEDGMENTS

We are grateful to Professor J. S. Mitchell and Professor N. M. Bleehen for their valuable criticisms in the design of the form; and to the East Anglian Regional Health Authority Clinical Research Committee for initial financial support. We particularly wish to record our thanks to Mr. P. Hammersley, Director of the Addenbrooke's Hospital Computer Unit, and members of his staff for their advice and co-operation in establishing the system, and to Mrs. P. Williams for all her assistance in its successful introduction and day-to-day running.

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T.N.M. Classification of Malignant Tumours, 1974. U.I.C.C. Geneva.

Book review

The Brain and the Eye. By E. H. Wood, J. M. Taveras and M. S. Tenner (in the series Atlas of Tumor Radiology, Ed. P. J. Hodes), pp. xiv+521, 155 illus., 1975 (distributed in the U.K. by Lloyd Luke [Medical Books] Ltd., Year Book Medical Publishers, Inc.), £27·00.

After one has attempted to assess whether a new publication succeeds in what it sets out to do, it is perhaps no less important to ask whether that aim is in itself worthwhile or not. I am not in a position to judge the practical value of the other volumes in this series, but I feel that, even at the relatively low price for a publication of this quality, few radiologists will feel that their library is drastically incomplete without this book.

It is divided into one chapter on the different types of neural tumour and the methods of neuroradiological diagnosis, another on plain skull radiographs, and then about 100 case descriptions. As is usual in American publications, the emphasis is very strongly on angiography, but plain film findings are illustrated in almost half the cases, as are pneumographic or positive contrast medium studies. Computerized axial tomography is referred to only in the introductory chapters. A number of the angiograms are by retrograde brachial injection, which is now largely outmoded, and very few of the studies are subtracted; the few examples included are hardly acceptable by modern standards. Very many of the illustrations of all types have an overall grey appearance, similar to those in the classical text by Drs. Taveras and Wood; this seems to be a result rather of the photographic processing than of a high-kilovoltage technique.

Another drawback shared with the earlier book by Drs. Taveras and Wood is the division of the cerebral lesions into: retro-, infra-, intra-, latero- and anterior and posterior supra-Sylvian. I should be most surprised to learn that the authors themselves utilize this cumbersome and largely unproductive scheme, and personally know of no-one who does so.

It may well be that in, say, bone or gastrointestinal radiology an atlas of tumour types has a useful role to play. However, the task of the neuroradiologist is in general different from that of other workers in our speciality, and his skills are directed towards detecting the presence of lesions rather than attempting to provide a histological diagnosis.

IVAN MOSELEY.

1976, *British Journal of Radiology*, *49*, 868–874

An on-line computer graphics terminal for radiotherapy treatment planning

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A programmed graphics terminal has been connected on-line to a large time-shared computer for calculating dose distributions in radiotherapy treatment planning and provides a viable alternative to dedicated systems and batch working. The terminal equipment is based on a mini-computer and includes a function-key device for outline input, a large-screen refresh oscilloscope for viewing results and an X-Y plotter for hard-copy. Radiotherapy dose computation programs in standard Fortran are stored and run on a large remote computer with graphical interaction at the terminal. External beam programs can calculate dose distributions for most commonly used treatment situations and can compute in off-axis planes. Data input is fully interactive and easy to understand. Dose distributions are displayed as isodose contours. Advantages of the system include accuracy, speed, ease of use and maintenance, and transferability of the programs between different host computers.

The advantages to be gained by the use of digital computers for calculation of dose distributions in radiotherapy treatment planning are now well accepted by those working in the field, and efforts in this direction have resulted in a multiplicity of approaches in both the nature of the programs for the computations and in the equipment on which the programs are implemented. Wood (1974) gives a useful survey of the field. At the present time three distinct types of implementation may be distinguished:

(1) off-line calculations using a large computer—so-called "batch" working, *e.g.* the "Glasgow" system (Hope and Walters (1964));

(2) "dedicated" systems, where the complete calculations are carried out on a local mini-computer. Several such systems are now commercially available, the most well known being RAD-8, based on the work of Bentley and Milan (1971);

(3) "on-line terminal" systems, which work interactively in conjunction with a large time-shared computer. Several systems of this nature have been developed in the U.S.A., *e.g.* those of Mohan *et al.* (1974), Ryden and Newton (1972) and Sternick *et al.* (1974).

Batch systems have the advantages of low capital outlay, and the calculation programs are usually written in a high level language; they suffer from delays in turn-round time and deficiencies in the mode of presentation of results. In contrast, dedicated systems provide the fast response and flexibility of interactive working and improved display of results, at the cost of high capital outlay and relative inaccessibility of the programs which are usually written in assembler language. (More recently work has been done to provide programs for dedicated systems written partly in high-level language.)

The on-line terminal approach attempts to combine the best features of each of the above, a relatively low-cost terminal being used to organise the interaction and display of results, with the computational load being shifted to a large remote machine where programs written in a high-level language can be efficiently maintained and run. This paper describes the first experiment in the U.K. to investigate the use of an interactive graphics terminal for radiotherapy dose planning. The experiment, sponsored by the Department of Health and Social Security, has been jointly carried out at the Middlesex Hospital, London, and Addenbrooke's Hospital, Cambridge.

THE TERMINAL

The local terminal equipment (Fig. 1) is required to perform four functions:

(1) interaction with the user;

(2) communication with the "host" time-sharing computer;

(3) generation and presentation of graphical and alphanumeric display; and

(4) provision of hard-copy of results.

An appropriately programmed mini-computer controls the organization of these functions which are carried out by attached peripheral devices (Fig. 2). The equipment configuration chosen for the experiment is based on a Varian 620/L mini-computer with 8 192 words of 16-bit memory.

The above functions are implemented as follows:

(1) interaction with the user is via an ASR33

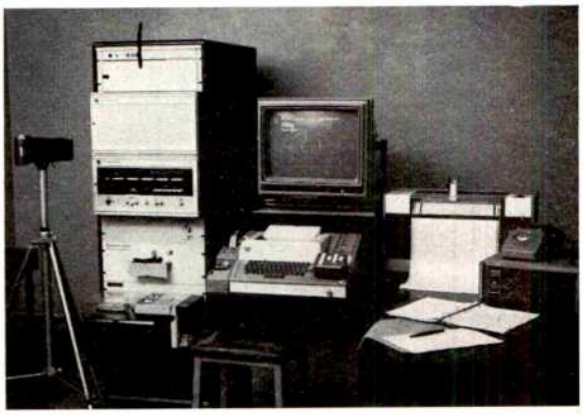


FIG. 1.

The terminal equipment, showing from left to right: the Polaroid camera; the computer cabinet containing the display processor, the mini-computer and paper tape system; the display oscilloscope and Teletype; the plotter; and the G.P.O. handset and modem.

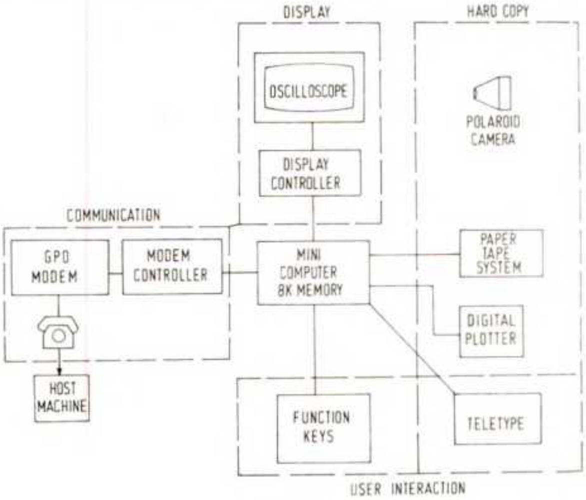


FIG. 2.

Schematic diagram of the components of the four functional areas of the terminal: user interaction, communication, display and hard-copy.

Teletype for textual input and a specially built function-key device for graphical input;

(2) a modem controller, G.P.O. Modem 1 and handset, provide a communications link with the host computer over the public telephone network;

(3) graphical display is provided by a Hewlett-Packard 1310A high-speed refresh oscilloscope, using a 26 cm square writing area. The display produced is in the form of straight line vectors which are generated by a display controller (Stabletron Vector Generator Model 1307/1) interfaced to the Varian computer;

(4) hard-copy is obtained using a Calcomp 565 digital incremental plotter at the Middlesex, and a U.C.C. "Midas" plotter and Polaroid close-up camera at Addenbrooke's. Additional textual hard-copy is provided by the Teletype, and a Varian high-speed paper tape system allows dumping and reloading of graphical results for later appraisal or hard-copy.

The program in the terminal occupies about 3300 memory locations (the remainder of memory being used for buffering textual and graphical information), and is organized in such a way that, in the first instance, the terminal appears to the user to behave like a typical visual display unit. When connected on-line to the host computer, the user communicates with it using the Teletype keyboard, the alphanumeric text appearing on the screen. Subsidiary tasks, such as provision of hard-copy, use of the paper tape system, etc., are initiated from the keyboard by typing control characters. Special sequences of characters received from the host computer initiate other tasks such as reception of graphical information and interaction using the graphics function keys. The terminal program, although designed with the needs of radiotherapy planning in mind, is independent of this application and could equally well be used for others.

THE HOST COMPUTER

The terminal may be connected on-line to any large computer which is capable of supporting a remote alphanumeric terminal in interactive time-sharing mode. A practical requirement is that the host computer be capable of transmission speeds of at least 30 characters per second (300 baud) so that interactions, especially those of a graphics nature, are not unduly slow. The host computer which has been used for the experiment is the Univac 1108 system run by the Scicon commercial bureau at Milton Keynes. The communications speeds used are 1200 baud from host to terminal and 75 baud in the reverse direction. The host computer is accessed by dialling a reserved telephone number.

Initially the user interacts with the operating system of the host in a standard manner to log on to the system, set up some files and initiate an applications program. Thereafter he interacts directly with the applications programs to produce treatment plans, and at the end of the session logs off the host computer in a prescribed manner and disconnects the telephone.

Host computer programs

The user spends the majority of his time on-line in direct communication with the planning programs. These programs have been written completely in standard Fortran, and their operation is almost entirely independent of the particular host computer being used. Where the terminal is called on to perform a task other than textual communication, *e.g.* reception of graphics by the terminal, this task is initiated and controlled by routines in the host computer which transmit coded sequences of characters to be interpreted by the terminal as control functions or graphical data. These routines are also written in standard Fortran: it should be noted that our system requires no modifications to the host operating system, and machine-dependent incorporations have been reduced to a bare minimum.

At the outset we envisaged two separate applications, external beam planning and interstitial planning; since the latter is still in the development stage at the time of writing (Jameson (1975)) we restrict ourselves in what follows to the external beam application which is now fully operational.

The External Beam Application

Our aim has been to provide a facility for external beam planning with the ability to compute dose distributions:

(1) for all commonly used megavoltage machines and energies;
(2) in isocentric or fixed source-skin distance (s.s.d.) treatments;
(3) for plain and wedged fields;
(4) with or without tissue compensators;
(5) in the presence of tissue heterogeneities (at present restricted to lung tissue);
(6) for arcs of rotation as well as fixed fields;
(7) in the plane of the central axes and also in parallel planes.

The planning task has been divided into two logical stages, each dealt with by a separate host program: firstly, the interactive creation or editing of a file of patient data, controlled by the INPUT/EDIT program; secondly, the computation of the dose distribution and interactive interrogation of this distribution to produce isodose contours or doses at specified points, controlled by the DOSE program. In practice these programs will be called in alternation one or more times to produce a satisfactory plan.

The essential features of each program are set out in the following sections; in both cases we have tried to exploit the fast interactive capabilities of the terminal to the full in providing visual confirmation (in textual or graphical form) at each stage of the task, since this substantially reduces the risk of error as well as providing a more natural "conversational" dialogue between user and computer.

The INPUT/EDIT program

To assemble or modify patient data the user interacts with the INPUT/EDIT program, and the nature of this interaction has deliberately been kept simple. The user is guided through a sequence of actions by making yes/no responses to questions asked by the program, and by providing additional information in the form of numerical parameters, text or manipulation of function keys as appropriate. Since all required information is solicited by the program, the user needs the minimum of expertise to operate it, and experience has confirmed that sufficient competence may be gained by an operator in a few hours.

The data required for a new patient consist of:

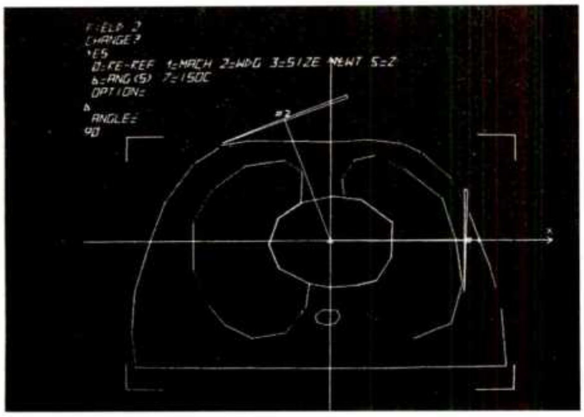
(1) patient identification and general settings (fixed s.s.d. or isocentric, use of compensators, etc.);
(2) patient outlines (surface contour, lung tissue, tumour volume, etc.) and the position and size of area over which to compute dose—the "window"; and
(3) details of applied fields.

Data (1) are provided through the Teletype keyboard.

Outlines (2) may be input either through the keyboard as manually digitized co-ordinates or from a transparency fixed to the face of the oscilloscope screen. In the latter case the transparency is prepared beforehand (perhaps reduced in scale from the original, using a pantograph). The outlines are then transmitted to the host computer by moving a graphical cursor cross to selected points on the outlines using the function keys. The window is defined either numerically or by function keys. At this stage the program transmits back to the terminal a picture of the outlines and window settings for confirmation and initiates the printing on the Teletype of a summary of information entered so far.

Parameters for each applied field (3) are then solicited individually: these include choice of machine and wedge, wedge orientation, field size, weighting and angle of application. After all parameters have been specified, a textual confirmation of settings is provided on the screen, together with a pictorial representation of the applied field superimposed on the outlines. Certain simplifying assumptions are made by the program initially (*e.g.* the coincidence of intersections of field axes and the placing of entry points of fixed s.s.d. fields on the patient surface) which cover the majority of plans; the user may now change these settings if inapplicable or, indeed, any other parameter (see Figs. 3 and 4). The cycle of change and confirmation is repeated until the user is satisfied, when the settings are printed on the Teletype and the next field (if any) is specified.

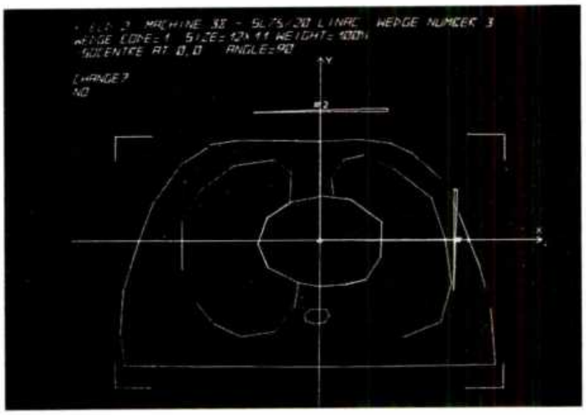
Having provided all the necessary data for the plan, the user may go back and edit any selected part, or go on to initiate dose computation by transferring to the DOSE program.



```
FIELD 2
CHANGE?
YES
 0=RE-REF  1=MACH  2=WDG  3=SIZE  4=WHT  5=Z
 6=ANG(S)  7=ISOC
 OPTION=
6
 ANGLE=
90
```

FIG. 3.

Editing a field. The user requests a change for Field 2, and is provided with coded options. He chooses option 6 (the angle) and inputs a new value (90 deg., measured anti-clockwise from the X-axis).



```
FIELD 2  MACHINE 3 - SL75/20 LINAC  WEDGE NUMBER 3
WEDGE CODE=1  SIZE=12X11 WEIGHT=100%
ISOCENTRE AT 0,0   ANGLE=90

CHANGE?
NO
```

FIG. 4.

The result of the change. Field 2 is redrawn at the new angle, the current settings of the field parameters are displayed, and a further opportunity to edit the field is provided. The user is now satisfied with the field, and types 'NO'.

The DOSE program

Once initiated, this program automatically computes the dose distribution on a rectangular grid coincident with the specified window. The dose contribution from each applied field is calculated according to the empirical model of Thomas and Haybittle (1975). Arcs of rotation are approximated by discrete fields at 10 deg. intervals. Correction for obliquity is made by the inverse square method of Garrett and Jones (1962) and the dose shift technique of Greene and Stewart (1965) is used to correct for heterogeneous tissue.

The method of Thomas and Haybittle has also been used to model the shape of the beams perpendicular to the plane of calculation, thus allowing dose distributions to be obtained in planes parallel to that of the central axes (or indeed for arrangements of non-coplanar fields or for wedges rotated by 90 deg. from their standard orientation). The parameters for the beam model are stored on a separate file, one set of 17 numbers for each machine/wedge combination.

When computation is complete, the program indicates the value of the maximum dose of the whole distribution on the screen, and prints out on the Teletype a table of dose levels expressed as percentages of this maximum. From now on the program is under the control of the user who may, by simple commands, request either one or more isodose contours to be drawn, specified either as percentages of the maximum or as computed dose levels (Fig. 5). He may also, if desired, request the value of the dose at particular points which he indicates using the function keys.

Having assessed the plan, the user may either recall the INPUT/EDIT program to make changes to the data, or make a hard-copy of the final plan using the camera and/or plotter. The complete Teletype print-out forms an accompanying hard-copy document. In addition, a paper tape may be punched which contains a record of the display present on screen; the display may be recovered at a later time by reading the tape back into the terminal. It is usually preferable to punch the successive plans of a session on a single tape for later off-line plotting, since plotting on-line takes a relatively long time compared with punching.

Advantages of the System

Accuracy

The greater inherent accuracy afforded by a large computer allows complicated mathematical expressions such as occur in our model to be evaluated with greater precision; cumulative errors in arithmetic

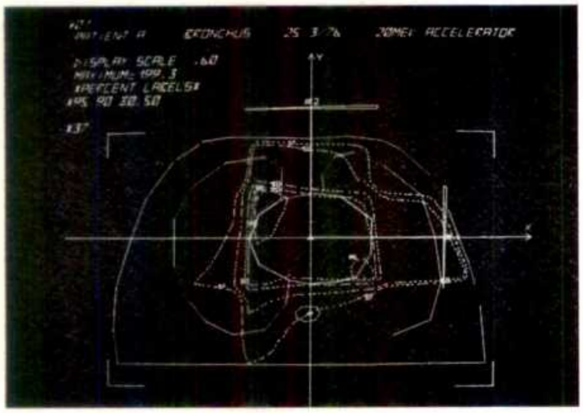


FIG. 5.

After computation of the dose distribution, the user requests isodose contours to be drawn (dotted lines). Here, the dose levels are expressed as percentages of the maximum, and contours have been requested at 95, 90, 80, 50 and 37%.

are also kept to a minimum. We must, of course, examine the accuracy of the model itself in comparison with measured data; this has been done for single fields by Thomas and Haybittle (1975) and Speller (1975), and the latter has also compared the results for complete plans with those calculated manually. The authors find that in the majority of cases the clinically acceptable targets of 2% accuracy in dose or 2 mm in position are obtained.

The accuracy of the final isodose map is dictated in part by the spacing between the individual points at which dose is computed. With the large memory available on the host machine we are able to compute most plans with a point spacing of 0.5 cm. We compute individual fields separately on a grid with 0.5 cm spacing perpendicular to the central axis and variable spacing along the central axis, allowing increased accuracy in the region of maximum dose curvature.

Speed

For the system to be acceptable in practice it must respond sufficiently rapidly to any user request for action. The speed of response in our system depends on a number of factors:

(a) speed of computation of the host programs;
(b) loading of the host computer due to other users; and
(c) speed of transmission of information to and from the host.

Most of the computations required during interaction with the INPUT/EDIT program are trivially small; the major computational load takes place during the DOSE program for calculation of the dose distribution and for generation of isodose contours. The host machine we currently use is very fast and efficient, and we have paid particular attention in writing the programs to maximizing their efficiency. In particular, the beam modelling methods used are well suited to rapid computation. For example, the computation of an isodose map for a three-field plan is accomplished in a fraction of a second of computer time.

Bearing in mind that we share the host machine with, typically, tens of other users, real-time response is an order of magnitude slower—a three-field dose distribution is computed in about four seconds real time. Other system overheads occasionally introduce delays, but these are also only of the order of a few seconds. A typical isodose contour can be drawn on the screen in five to ten seconds. The slow transmission speed of 7.5 characters/second from terminal to host is not a limitation since it is still faster than the typing speed of the operator. Transmission from host to terminal at 120 characters/s provides rapid reception of text with writing speeds, in graphics mode, of up to 63 cm/s.

Detection and correction of errors

User errors are kept to a minimum in two ways. At important points in the programs consistency checks are incorporated which detect erroneous input parameters, inform the user of the error and allow re-input. To check every item of input for all possible errors would result in unacceptably large programs and we therefore adopt the technique of confirmation of input data wherever possible in graphical form so that errors are immediately apparent: for example, a misplaced outline point will be detected when the outline is drawn on screen, a wedge with the wrong orientation can be spotted when the field is drawn graphically, and so on. After each confirmation the user must indicate whether the data is valid before proceeding further; if an error is indicated he may make an immediate change to correct it.

Errors may also occur during transmission to or from the host machine due to noise on the communications link. In practice errors in transmission to the host are relatively few because of the small data volume and the slow speed of transmission: they manifest themselves as "typing errors" which are detected by the program.

Conversely, transmissions of graphical data from the host are most prone to noise errors since large volumes of data are being transmitted at a fast rate.

Each graphics transmission contains redundancy checks generated by the host and monitored by the terminal. The nature of these checks is such that it is impossible for a graphics transmission error to go undetected by the terminal. After each graphics transmission the terminal must inform the host whether the data was received correctly or not; if the host is informed of an error it performs a re-transmission. The whole process of graphics error correction is automatic and needs no user intervention.

Experience has shown that, on a dial-up connection, one may occasionally establish a "bad-line", when occurrence of errors is unacceptably frequent. In these cases the user is advised to abort the connection and re-dial to get a better line.

Ease of use

We have already seen that the features of host-directed input procedures and interactive confirmation and error checking provide a readily assimilated environment for treatment planning, reducing education in using the system to a minimum and leading to a faster throughput of error-free plans.

Ease of maintenance

The programming of the terminal, being independent of the application, has required very little maintenance and has remained essentially static throughout the experiment. The radiotherapy programs have evolved in the light of experience and we have shown that changes have been particularly easy to incorporate because the programs are stored on the host machine in high-level language form and we have the use of sophisticated program development and debugging aids. In practice we have been able to perform modifications speedily and without interrupting routine service. Because program resources are shared, any modifications are immediately effective at each centre using the system, and in this way uniform standards are automatically maintained. Provision of new machine data or changes to existing data are particularly easy to perform, and again may be made in parallel with routine operation.

Interchangeability of host computers

The radiotherapy programs, being written in a standard high-level language, may be implemented on most time sharing computers. We have, in the course of the experiment, transported the system and run it on five separate host machines with very few problems. Although we currently use a commercial bureau for routine use, we have successfully implemented the system on two Health Service machines (an ICL 1904S and a Rank Xerox Sigma 6).

CONCLUSIONS

After over a year of routine use the system has been very favourably received by planning staff at both our hospitals and has replaced existing manual and computer methods of treatment planning. Plans are more rapidly and accurately produced and it is now feasible to prepare alternative plans or those for more elaborate arrangements of fields within a sensible time scale.

Since the start of the experiment, availability of computer hardware has changed considerably and we would now alter the configuration of the terminal in further developments of the system. We are aware that the lack of a tablet digitizer for outline input is a disadvantage of the present system, and that the paper tape devices could be replaced by a low cost magnetic medium. Even after including such items, a preliminary costing indicates that an improved terminal could be purchased for about half the cost of a competitive dedicated computer.

It has always been our intention to use Health Service computers to support our application and this aim is currently coming to fruition, thereby allowing a considerable reduction in running costs. It is our firm belief that a network of programmed terminals sharing the resources of a large computer will provide a most effective tool for scientific computing activities in hospitals, both in the field of radiotherapy and in other disciplines.

ACKNOWLEDGMENTS

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Book review

Health Protection of Radiation Workers. By W. Daggett-Norwood, pp. 442, 1975 (Illinois, Charles C. Thomas), $27.50.

The author of this book has had a distinguished career in the medical care of radiation workers in the atomic energy industry from its very early days in the 1940s.

The cover note to the book claims that it is addressed to physicians and nurses, teachers, health physicists, occupational hygienists, public health officers, safety specialists and biologists and that it will help educate the public as to the hazards of radiation.

Although the book apparently covers the necessary ground, much of it is superficial and oriented towards the nuclear power programme of the United States. Those chapters concerned with medical topics of which the author has direct experience are well done and should be read by anyone with an interest in the medical care of radiation workers. Those with some knowledge of radiation protection will find the book interesting, but it is likely to confuse the uninitiated.

The first four chapters of the book present an account of the physics, the measurement, the dosimetry and the general biological effects of ionizing radiation. They are done badly, and the physics is often misleading. For instance, in the description of the use of photographic film for radiation measurement it is stated that "Charged particles transversing the photographic film become trapped in the silver crystal lattice, and form a latent image". In the following chapters the author is on surer ground in describing the acute, late and genetic effects of radiation in humans. Few concessions are made to those without a medical or biological background. In the chapter on acute effects, data from nuclear and other radiation accidents as well as data from accidental exposures to weapon fall-out are quoted. Brief descriptions of the accidents would have added greatly to the book, but are not given. The dose units are given variously as rads, epigastric rads, reps, rem and r. In the chapter on late effects, entitled "Somatic Effects of Radiation other than Those due to the Acute Radiation Syndrome", the distinction between RBE and quality factory becomes confused. The chapter on genetic effects draws heavily on the U.N.S.C.E.A.R., B.E.A.R., and B.E.I.R. reports. The eighth chapter summarizes the radiation protection standards and regulations of the I.C.R.P., N.C.R.P., and A.E.C. Chapter nine is a very brief summary of the basic elements of radiation protection. The sub-headings of this chapter proceed from "Melting of Reactor Fuel Elements" and "Tornadoes" by way of "The Pocket Dosemeter" to "Plant Specifics" and "Need for Exposure Records". The next two chapters give excellent summaries of the use of medical examinations in the supervision of radiation workers and the techniques of removing radionuclides from the skin and body. Chapter twelve is an informative summary of the metabolism of a variety of radionuclides, excluding plutonium and other transuranium elements which are dealt with in the thirteenth chapter. Both these chapters, like those on the somatic effects of radiation, are well referenced, although rather devoid of any effective comment by the author. The next chapter of the book deals with the planning for radiation accidents. The fifteenth chapter gives a sketchy outline of the necessity for a nuclear power programme and the methods of dealing with the radioactive wastes that it will generate. This illustrates one of the weaknesses of the book which gives virtually no attention to the problems of workers using radiation in industry or in medicine other than in the nuclear power industry. The final chapter deals rapidly with the problems of becoming an expert witness in cases of industrial injury due to exposure to radiation and with the recommendations of a U.S. National Commission on States Workmens Compensation.

The author has been badly served by his publisher. The book is full of misprints and the distinction between different categories of sub-headings is not always clear.

An authoritative text on the health protection of radiation workers is certainly needed; unfortunately this book is not it.

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1976, *British Journal of Radiology*, *49*, 875–879 OCTOBER 1976

Persisting cyclic ovarian activity in cervical cancer after surgical transposition of the ovaries and pelvic irradiation

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ABSTRACT

The effect of surgical transposition of the ovaries on gonadal function was investigated in ten young women with carcinoma of the uterine cervix, stages I and II. Gonadotrophin-, oestradiol- and progesterone-levels were determined before and during pelvic irradiation. A control group consisted of seven patients with cervical cancer who did not undergo ovarian transposition. In the control group gonadotrophins began to rise after radiation doses of 560–2400 rad (FSH) and 1130–2600 rad (LH) respectively.

The excessive secretion was not seen in patients who had ovarian lifting. Ovulatory cycles occurred during or after pelvic irradiation in seven women of the study group, either spontaneously or induced by clomiphene treatment. This indicates that transposition preceding radiotherapy is an effective means of preserving ovarian secretion in young women in whom malignancies of the pelvic region demand irradiation.

It has been accepted as inevitable in the past that females receiving irradiation for cervical cancer were permanently deprived of ovarian function.

Since the late fifties, clinicians have been increasingly aware of the value of retained ovarian function in young women with curable malignancies demanding irradiation of the pelvic region (Kovacev, 1968; Krebs *et al.*, 1963; McCall *et al.*, 1958; Trueblood *et al.*, 1970). Efforts to preserve the ovaries were initiated by increasing evidence that castration often caused serious deficiency symptoms in young women such as decalcification of bone tissue, premature development of atherosclerosis and local genital changes (Fraser and King, 1957; Griffith, 1956; Masters, 1957). Several procedures have been devised to transpose the ovaries from the irradiated field (Krebs *et al.*, 1963; Kovacev, 1968; Trueblood *et al.*, 1970).

In general, the endometrium does not show cyclic changes after irradiation; the presence of an oestrogen effect after transposition had to be judged by indirect tests of ovarian function such as cytological findings in vaginal smears, basal body temperature chart, etc. In this article we provide evidence that the secretion of ovaries and pituitary gland is still adequate for the production of mature follicles and corpora lutea after ovarian lifting and pelvic irradiation.

In this department, where cervical cancer is frequently seen, young women in whom reliable substitution therapy seems doubtful are now informed that operative procedures for ovarian preservation are available.

It was the aim of this study to investigate whether ovaries positioned away from the irradiated field would continue to function normally. Ovarian function was monitored by frequent serum gonadotrophin, oestradiol and progesterone measurements both before ovarian transposition as well as during and after irradiation.

METHODS

Patients

The study group comprised ten women, 26–34 years of age, with cervical cancer, stages IB to IIB (Table I). Seven patients, 26–36 years of age, who did not undergo ovarian transposition before irradiation, served as control. These patients had cervical cancer, stage IIA (1 case), IIB (2 cases), III (3 cases), and IV (1 case) (Table II).

Operation

The principle of the operation is to position the ovaries, with their vascular pedicles intact, out of the pelvis and away from the field of irradiation. After dividing the round ligament, the leaves of the broad ligament are separated digitally, and the fallopian tube and ovarian ligament are divided at their uterine ends. By lifting the tube and ovary, the peritoneal leaves can easily be incised upwards along and below the ovarian vessels, creating a long, vascular ovarian pedicle. The sigmoid on the left, and the ceacum on the right, are now pulled medially, and the posterior peritoneum is incised lateral to these.

The entire ovarian vascular pedicle can then be mobilized retroperitoneally, and the ovaries are

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TABLE I

Ovarian function before and after irradiation in patients with ovarian transposition

Patient	Age	Stage	Ovulatory cycles observed			
			Before treatment	After transposition	After transposition during irradiation (dose received in rad)	After clomiphene (dose received in rad)
J.N.	26	IIB	+	+	—	+(3000)
N.S.	30	IIA	+	—	—	—
K.N.	31	IIB	—	+	—	not done
K.M.	31	IIB	—	—	—	+(6000)
R.M.	31	IIB	—	—	—	+(6000)
A.K.	29	IB	—	—	—	+(6000)
D.M.	34	IIB	—	—	+(2700)	+(3600)
B.T.	29	IIA	+	—	+(1200)	not done
E.N.	32	IIB	+	—	—	not done
R.N.	26	IIB	—	—	+(1800)	not done

TABLE II

Changes of oestradiol– and gonadotrophin-levels during irradiation in patients without ovarian transposition

Patient	Age	Stage	Ovulation observed before irradiation	Oestradiol (E_2)		Lowest level attained (pg/ml)	Gonadotrophins	
				Dose at which E_2 began to decrease	Dose at which follicular phase levels were attained		Dose at which levels increased	
							LH	FSH
L.L.	26	III	—	1130	3200	10	1130	1130
J.M.	26	IIB	—	770	3500	25	1700	770
F.B.	36	IIB	—	560	840	<10	1700	560
E.B.	26	III	+	1200	2700	10	2400	1800
S.B.	32	IIA	—	—	—	20	—	—*
B.M.	32	IV	+	640	4500	20	1280	640
S.M.	36	III	—	—	—	10	2600	2400†

*This patient received 6000 rad by intracavitary radium alone. The gonadotrophin and oestradiol levels were in the castrate range in blood samples taken one week after this treatment.

†Low oestradiol levels (10–20 pg/ml) were found throughout the investigative period.

similarly positioned retroperitoneally on the posterolateral abdominal wall. The peritoneum is then carefully closed.

Radiotherapy

Two to three weeks after ovarian transposition radiotherapy was instituted. In all patients a total dose of 6000 rad was given.

Three patients of the study group received first external irradiation followed by intracavitary application of radium. In one of these patients (A.K.) ^{60}Co irradiation was given through eight fields, 10×4 cm each, four anterior and four posterior directed towards point B and the central area protected with lead. In the other patients ^{60}Co irradiation was given through two lateral moving beam fields each of 120 deg. (*i.e.* from 30 deg. to 150 deg. and from 210 deg. to 330 deg.). The approximate volume receiving 90–100% of the dose is indicated in Fig. 1. Weekly tumour doses of 900–1200 rad were given in 3–5 fractions. The patients of the control group were treated with ^{60}Co alone according to the same regimen except patient S.B. who received intracavitary radium alone.

Hormone Assays

Luteinizing hormone (LH) and follicle stimulating hormone (FSH) were measured by radioimmunoassay using double antibody techniques (Odell *et al.*, 1967) with the second antibody fixed to cellulose. The material was obtained from CEA, Sorin, Italy. Results are expressed in mIU/ml in

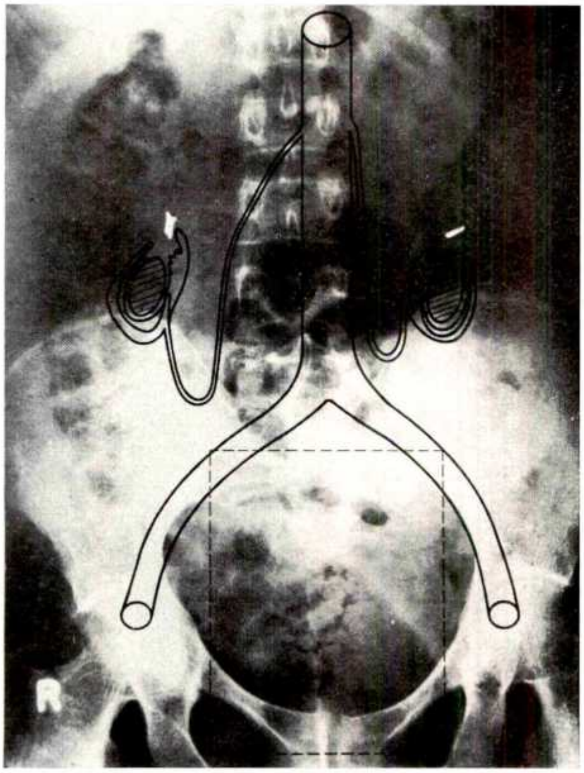

Fig. 1.

Position of the lifted ovaries. Radio opaque tags were placed near the uterine pole of the ovaries. The ovaries were lifted a distance of 14–16 cm from their normal position. This causes a reduction of the ovarian dose to 1–3%. The approximate volume receiving between 90 and 100% of the dose is indicated by the hatched rectangle.

terms of the reference preparation 68/40 (LH) and 68/39 (FSH) of the Medical Research Council, Mill Hill, London.

Oestradiol levels of the study group were measured in the diethyl ether extracts of 100–200 μl of plasma without chromatographic separation of oestrogens (Hotchkiss *et al.*, 1971). In the control group, where oestradiol usually reached lower levels, the diethyl ether extracts of 2 ml plasma specimens were chromatographed on small Sephadex LH-20 columns using iso-octane/benzene/methanol (62/20/18) as eluting solvent. The antiserum purchased from CEA, Sorin, Italy was rather specific, having a cross reaction of only 3% with Oestrone and 0.5% with Oestriol. 10 pg could be significantly differentiated from zero.

Progesterone was measured in petroleum ether extracts of plasma by radioimmunoassay according to Abraham *et al.* (1971). The antiserum was purchased from "Biolab" Belgium. It had a 7% cross reaction with 17α-hydroxy-progesterone, the steroid that showed most interference.

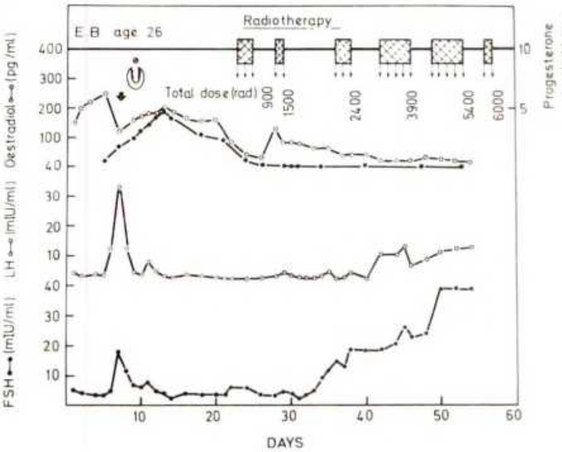

Fig. 2.

The curves of (from top to bottom) oestradiol-, progesterone-, LH- and FSH-levels during the investigative period are shown. One ovulatory cycle is seen before radiotherapy. This is indicated by the ovulatory surge of LH and FSH on day 7 followed by quantities of progesterone which are consistent with the formation of a mature corpus luteum. On day 23 irradiation was instituted. After a total dose of 1200 rad oestradiol began to fall, after 2400 and 1800 rad LH and FSH respectively began to rise.

Clomiphene stimulation: In six patients of the study group stimulation of gonadotrophin secretion was attempted by a five day course of clomiphene (5 × 100 mg). This normally initiates follicular maturation and some days later ovulation. Clomiphene treatment was not used in the controls since their increasing gonadotrophin levels indicated that the ovaries had become irresponsive under irradiation.

RESULTS

The changes of oestradiol and gonadotrophin secretion in peripheral blood during irradiation without preceding ovarian transposition are demonstrated in Table II and Fig. 2.

The characteristic gradual gonadotrophin increase into the castrate range is caused by the negative feedback mechanism after cessation of the oestrogen depressant effect. The increase of FSH usually precedes LH-elevation. Oestradiol levels began to fall after irradiation doses between 560 and 1130 rad. Usually the oestradiol secretion did not cease altogether in the controls during the investigative period. It fell only into the range normally seen in the early follicular phase of the menstrual cycle, *i.e.*

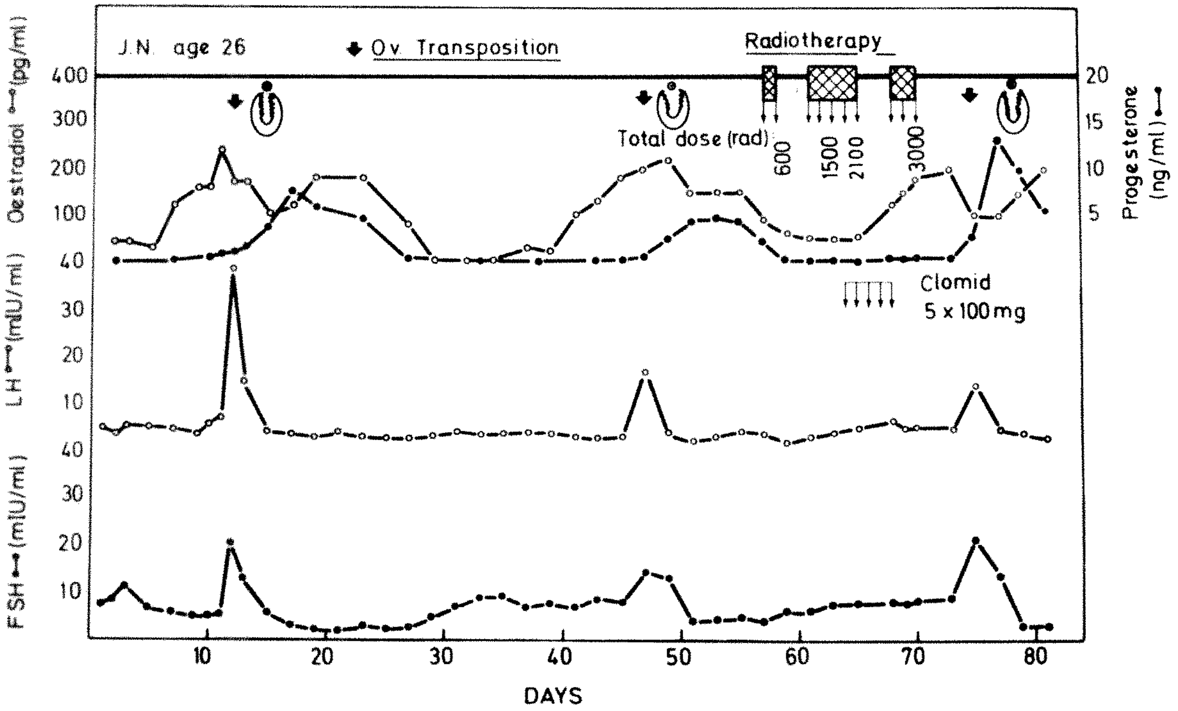

FIG. 3.

This patient had a normal ovulatory cycle before ovarian lifting and also a spontaneous cycle after the operation (days 12 and 47 respectively). When the patient had received 3000 rad to the pelvic region ovulation occurred after clomiphene treatment (day 75).

20–40 pg/ml. Gonadotrophin secretion reached levels of 27–160 mIU/ml (FSH) and 12.6–27 mIU/ml (LH) after 6000 rad in the control group.

The excessive secretion of gonadotrophins was not seen in the patients who had ovarian transpositions. In many cases the cyclic ovarian secretion persisted despite transposition and subsequent pelvic irradiation (Table I). Five patients had spontaneous ovulations after transposition of the ovaries, three of them after having received radiation doses of 2700, 1200 and 1800 rad respectively. In six patients clomiphene-citrate was given at the end of or after radiotherapy. In five of them LH/FSH was raised, initiating increased oestradiol production, ovulation and corpus luteum formation. Three of these five patients had received the full dose of 6000 rad at this time. In two patients gonadotrophin levels remained low after transposition, without signs of cyclic ovarian activity. In these patients, however, ovarian secretion must have remained above the level of the hypothalamic sensor element for oestrogen, controlling the negative feedback mechanism. One illustrative case is demonstrated in Fig. 3.

Aortography was performed on two patients four weeks after ovarian transposition, to demonstrate the function of the ovarian arteries. In both cases the ovarian arteries were patent and could be followed along their new course.

DISCUSSION

Two reservations have been expressed about ovarian preservation in patients with cervical cancer: (1) that the ultimate result of therapy might be adversely affected by persisting ovarian secretion and (2) that early metastasis to the ovaries may occur making preservation hazardous (McCall *et al.*, 1958). Survival figures of several published series indicate, however, that the presence of the ovaries has no influence on the percentage of cures obtained (Krebs *et al.*, 1963; Webb, 1975). Metastasis into the ovaries is apparently extremely rare in cervical cancer since authors of some large published series fail to mention it (Henriksen, 1949; Brunschwig and Pierce, 1948).

The plotted values of gonadotrophins and gonadal steriods sufficiently demonstrate the effectiveness of ovarian transposition for preserving ovarian function in patients where malignancies of the pelvic region demand radiotherapy. Cyclical ovarian secretion often persisted after surgical lifting despite irradiation and manipulation of the ovaries during the operation. This is surprising since the mechanism controlling ovulation is known to be highly susceptible to environmental and emotional factors. The characteristic high post-castration secretion of gonadotrophins never occurred after ovarian transposition, demonstrating the intact depressant effect of ovarian oestrogens.

CONCLUSION

The possibility of preservation of ovarian function should be remembered in cases of young women with curable malignancies in the pelvic region. Preservation is of particular value in patients who are difficult to impress with the necessity of replacement hormonal therapy to avoid acute castration symptoms, local genital changes and premature senescence, or when such régimes are difficult to control.

The technically simple operation described offers considerable chances of continuing cyclical ovarian function in young women.

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Book review

Sealed Radioactive Sources: British Standard (*BS5288/1976*), pp. 11, 1976 (London, British Standards Institution), £3·10.

This specification, which replaces the earlier *Specification for Gamma-Radiography Sealed Sources: BS3513*, refers to sealed sources used in medical, laboratory and industrial applications and specifies the requirements and characteristics of sealed radioactive sources as well as the essential performance and safety testing methods for particular applications. The specification which is concerned with the safe use of radioactive sealed sources is stated to be consistent with the requirements of the relevant, but as yet unpublished, I.S.O. Documents. It is also stated to be in agreement with the relevant I.C.R.P. and I.A.E.A. safety publications.

The first brief section defines the scope of the document and defines the special terms used. The second section specifies the general requirements, the production tests (*i.e.* testing of freedom from contamination and leakage), the source marking and associated certification. The final, third section specifies the tests which must be undertaken to evaluate the safety of the sources under working conditions. These comprise exposure to abnormally high and low temperatures and pressures, mechanical impact, vibration and mechanical puncture. Each test can be applied in several degrees of severity which is determined by the character and intended use of the source. The criterion of pass or fail depends on leakage of source contents. Details of the equipment used, the test procedures and evaluation of the result are given.

The text is supported by five appendices which provide detailed information concerning the nature and severity of the test to be applied depending on the source character and intended use; and procedures for leakage detection. The format of the source certificate is given.

Although the specification is of prime interest to source manufacturers the information contained in this specification will be of interest also to users of radioactive sources and will demonstrate the great care which needs to be taken to ensure the maintenance of the "enviable record of safe usage". It is surprising that in spite of recommendations given in other documents no recommendation is given here concerning the need to repeat at least some of the tests during the lifetime of the use of the source. It is to be hoped that all users will recognize the need for regular leakage testing especially when damage may be possible or suspected.

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1976, *British Journal of Radiology*, *49*, 880–882

A comparison between combined neutron- and telecobalt-therapy with telecobalt-therapy alone for cancer of the bronchus

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Abstract

The difference in response of human tumours to high and low LET radiation has been investigated in a series of inoperable, histologically confirmed bronchial carcinomas. One hundred and forty-nine were treated with low LET radiation alone (^{60}Co γ rays) and 108 with a combination of γ rays and fast neutrons of mean energy 6 MeV, one-fifth to one-third of the effective dose being from neutrons. The response was analysed by histological examination of the autopsy specimens. Tumour cell destruction was found to be significantly greater in the neutron-treated series. The two series were not strictly randomized but were closely similar to terms of tumour volume, histological grade and total treatment time. The sequence of treatments with neutrons and γ rays (N–γ, γ–N, γ–N–γ) was found to have no influence on the results.

In April 1972 we started radiation treatment with fast neutrons using a Soviet cyclotron of type U 120. In co-operation with the Zentralinstitut für Kernforschung, the Zentralinstitut fur Molekularbiologie of the Academy of Sciences of the GDR and the Medical Academy of Dresden, this apparatus, previously used for fundamental physical research, was reorganized for the irradiation of patients and the necessary dosimetry was implemented. The cyclotron provides neutrons of mean energy 6.2 MeV with a dose-rate of approximately 20 rad/min at a distance of 1 m (Eichhorn and Lessel, 1974). Since the cyclotron is 250 km from our institute we can only use it periodically. Up to the present 334 patients have been irradiated.

Aims and Methods

The qualitative differences in the response of cellular and animal systems to radiations of high and low LET are well known from radiobiological experiments. Our aim is to examine the importance of these differences in the radiotherapy of malignant disease in humans. For this purpose we have mainly irradiated tumours causing a high mortality rate due to metastatic spread, such as inoperable cancers of the bronchus, so that we can assess the radiation effect on the primary tumours by histological examination of autopsy specimens.

These specimens have been examined intensively by our pathologists using both macroscopic views and by means of numerous microscopic sections. The frequency with which the specimens are reported to be histologically free of tumour cells, only scar and necrotic tissue being present, has been compared in two series of patients, an earlier series treated with ^{60}Co γ radiation only and the other with a combination of fast neutrons and γ rays. This is a retrospective comparison rather than a randomized one. However, the two series are closely similar in terms of histological grade, tumour volume before irradiation and total treatment time (see below and Table II).

To avoid misunderstanding we must point out that our histological examination does not, of course, prove the complete destruction of all tumour cells. For that, an impossibly large number of serial sections would be required. But it is considered to be a constant measure of a massive reduction of the tumour-cell population, since the same method has been in use for many years.

As a rule we have given only part of the whole treatment by neutron therapy, namely one-fifth to one-third of the effective tumour dose, the remainder being given by ^{60}Co γ rays. This procedure is based partly on factors outside our control as explained previously (Eichhorn *et al.*, 1974), but above all it rests on the hypothesis discussed in the literature that the destruction of part of the anoxic radioresistant tumour-cell population by neutron therapy will lead to reoxygenation, and consequently to a radiosensitization of the remaining cells which can then be destroyed by irradiation with γ rays.

For the determination of the total effective tumour dose from the combined neutron and γ-ray therapy, the neutron dose has been converted into 'equivalent Röntgens', $R^* =$ neutron rad $\times$ RBE, according to an RBE-curve compiled from the bibliography and from own work (Magdon, 1975). For our tumour doses of 40 to 90 rad per daily fraction we used RBE factors of 3.5 to 2.6. All irradiations were given five times a week. Between the neutron and telecobalt therapy there was usually an interval of three to

TABLE I

PATIENTS AND TREATMENTS GIVEN

Group	No. of patients	Radiation given	Dose ± 1 Standard Deviation			
			$D\gamma$ (R)	D_n (rad)	$R^* = D_n \times$ RBE	$D\gamma + R^*$
I	149	γ only	7044 ± 904	—	—	7044 ± 904
II	36	neutron + γ	3354 ± 685	676 ± 80	1866	5220 ± 664
III	72	neutron + γ	4577 ± 451	381 ± 77	1007	5584 ± 471
IV	3	neutron only	—	762 ± 39	2175	2175 ± 74

TABLE II

COMPARISON OF THE GROUPS AND RESULT OF ANALYSIS OF AUTOPSY SPECIMENS

Group	Tumour volume before treatment ±1 Sd (cm³)	Total treatment time ±1 Sd (days)	Autopsy specimens histologically negative No.	%	Probability compared to γ rays only
I	212 ± 145	52 ± 12	47	32	—
II	260 ± 121	55 ± 13	21	58	< 0·01
III	216 ± 218	61 ± 19	35	49	< 0·05
IV	216 ± 106	24	2	67	—

TABLE III

EFFECT OF SEQUENCE OF NEUTRON AND γ-RAY TREATMENTS

Sequence		n–γ	γ–n	γ–n–γ
No. of patients		54	11	43
autopsy specimens histologically negative	No.	28	5	23
	%	52	45	53

eight days, but sometimes 18 to 30 days to give time for reoxygenation. Treatment plans have been made for all patients on the basis of anatomical cross-sections and the dose distributions have been calculated by computer. Treatment positions were checked by taking neutron radiographs (neutrograms) during therapy.

To sum up, the main criterion of our study of neutron therapy is the comparison of the radiation effect on the tumour as seen in the autopsy specimens of patients treated with and without neutrons.

RESULTS

The number of patients and the doses given are shown in Table I. In Group II the neutron treatment contributed 36% of the effective dose and in Group III 18%. Table II gives the results of the analysis of autopsy specimens together with a comparison of the groups in terms of total treatment time and tumour volume before treatment. The proportion of autopsy specimens found to be histologically negative was significantly greater in the neutron-treated series than in the series treated by γ rays alone. In other respects the groups were very similar, except that Group IV was treated in a shorter time (neutrons only, three patients). Table III shows the findings in the series given combined treatment, divided according to the order in which the two types of radiation were given.

DISCUSSION

Table II shows that the greater effect of the combined treatment cannot be due to a difference in tumour size in the two series. In addition, the total treatment time was rather longer for the combined treatment than for treatment by γ radiation alone. The total effective tumour dose in the combined treatment was smaller than the dose in the series

TABLE IV

RESULTS ACCORDING TO HISTOLOGICAL GRADE

	γ alone				neutron + γ			
	Patients		Autopsy specimen negative		Patients		Autopsy specimen negative	
	No.	%	No.	%	No.	%	No.	%
Well differentiated	94	65	28	30	68	63	36	53
Undifferentiated	51	35	19	37	40	37	20	50
Total	145	—	47	32	108	—	56	52

treated by γ rays. Thus the effect of the neutron beam on the tumours was substantially greater than one would have expected on the basis of the RBE values assumed. These RBE values were measured with cell cultures *in vitro*; human tumours *in vivo* evidently show a greater RBE.

Table IV shows the results classified according to the histological grade of the tumour. The proportion of the patients in the two grades is the same in both series. The improvement in the results of treatment by neutrons is similar for both histological grades.

Table III shows that the order in which the two types of radiation are given does not affect the result. This is not in agreement with the theory that it is best to give neutrons first so that part of the hypoxic population of cells can be killed, followed by reoxygenation of the remainder which can then be treated successfully with γ rays. On the other hand it could also be argued that neutrons given after γ rays might be able to kill the residual hypoxic cells which would have remained radio-resistant to further irradiation by γ rays.

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Book review

Computed Tomography of the Brain and Orbit (EMI Scanning). By P. F. J. New and W. R. Scott, pp. xiii+486 (illus.), 1975 (Baltimore, Maryland, Williams & Wilkins Co.), $39.50.

Computer tomography has had a profound impact on the practice of neuroradiology and upon the clinical management of patients with neurological and neurosurgical disorders. Since the first presentations by Hounsfield and by Ambrose in 1973, progress has been swift.

Major modifications to scanning equipment have provided faster, higher resolution scans, computer technology has made it possible to reconstruct the image in a variety of planes, significant advances have been made by the further use and understanding of contrast enhancement and the method has been applied in the quantitative study of tissue composition.

In such a rapidly changing scene the production of a hardback text is a formidable undertaking even though some fundamental principles remain unchanged. Drs. New and Scott have produced the first book of any note on computer tomography in the form of an atlas of pathological processes. This atlas is preceded by a general descriptive section incorporating basic physical, technical and anatomical information. Illustrated plain sections together with anatomical diagrams in the form of acetate overlays are provided as aids to orientation.

A wide range of pathological processes are depicted, many of them on the old 80 × 80 matrix but frequently correlated with conventional neuroradiological procedures and pathological specimens. The clinical features and operative findings are presented with each case. Much of the clinical material is from the Department of Radiology in the Massachussetts General Hospital from which department many valuable contributions on the subject have already been made.

This well-produced book was completed during 1975 and commendably contains the references almost up to the date of publication. It must be concluded, nevertheless, that those fortunate enough to be actively concerned with the revolutionary new imaging method will find this presentation and bibliography already dated. For those who are just entering the field of computer tomography and for some postgraduate students it should, however, provide a helpful introduction. The current literature must continue to be essential reading.

IAN ISHERWOOD.

1976, *British Journal of Radiology*, *49*, 883–886 OCTOBER 1976

Field shaping in electron beam therapy

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(*Received March, 1976*)

ABSTRACT

In the treatment of superficial lesions with 8–13 MeV electrons, lead shields are often used to protect the underlying tissue. Measurements were made with film and ion chamber to analyse various aspects of external and internal shielding in electron beam therapy. Data were obtained on the thickness of lead required for shielding, the effect of blocking on dose-rate, electron-backscattering from lead and X-ray contamination. Practical applications of a lead clay for shielding are discussed.

The treatment of superficial tumours with electron beams sometimes requires considerable beam shaping. Although circular and rectangular cones of various sizes are usually available, lead cut-outs are often needed to give shape to the treated area and to protect the surrounding normal tissue or a critical organ. In situations such as treatment of lesions in the lip or buccal mucosa, additional shielding is required to protect the internal structures beyond the treatment volume.

This paper discusses the problems of external and internal shielding in the radiotherapy of superficial lesions with 8–13 MeV electrons.

APPARATUS AND PROCEDURE

The electron beams of energy, 8, 10, 12, and 13 MeV used in this investigation were produced by the Toshiba linear accelerator, Model LMR/13. The doses were measured with two dosimetry systems, ionization chamber and film. The former was a 0·6 cm^3 Farmer chamber with the Capintec Digital Exposure Meter, Model 192. The film was Kodak RP/V. The characteristics of this film for electron beam dosimetry have been discussed by Feldman, *et al.*, (1974).

The response of film exposed to the electron beam at various depths in a polystyrene phantom ($\rho = 1{\cdot}05$ g/cm^3) was compared with the ion chamber measurements. An automatic rapid processor was used to process the films. Optical densities were obtained with a Macbeth Densitometer (TD–500, aperture size 1 mm). For related data, films were processed sequentially to minimize variations in processing conditions. Optical densities were converted into doses using sensitometric curves obtained as controls. These curves did not change significantly for different films from the same batch and when processed at different times.

The chamber measurements were made in the polystyrene phantom. The depths were corrected for displacement, perturbation (Harder, 1968), and changes in C_E with depth (I.C.R.U., 1972).

The results of the film versus ion chamber are given in Fig. 1.

Figure 2 explains the three types of arrangement used in the experiments involving the film. The arrangement (Fig. 2A) was used for relative depth-dose measurements described above. Figure 2B illustrates the arrangement used to obtain transmission data for lead as well as the values for the electron back-scatter at the interface. In the latter case the lead was placed inside the phantom directly behind the film. Figure 2C was the arrangement to obtain the range of the back-scattered electrons and the modifications of the depth-dose distribution caused by these electrons.

RESULTS

External shielding

1. Thickness of lead shielding. Figure 3 shows the dose at the phantom surface as a function of thickness of overlying lead. An important consideration in electron beam shielding is to make certain that the thickness is adequate to reduce the surface dose to an acceptable value. As seen in Fig. 3, if the

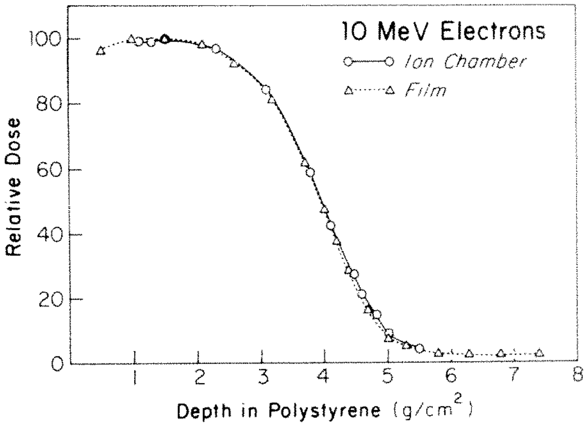

FIG. 1.

Comparison of film response with ion chamber measurements of relative depth dose for electrons.

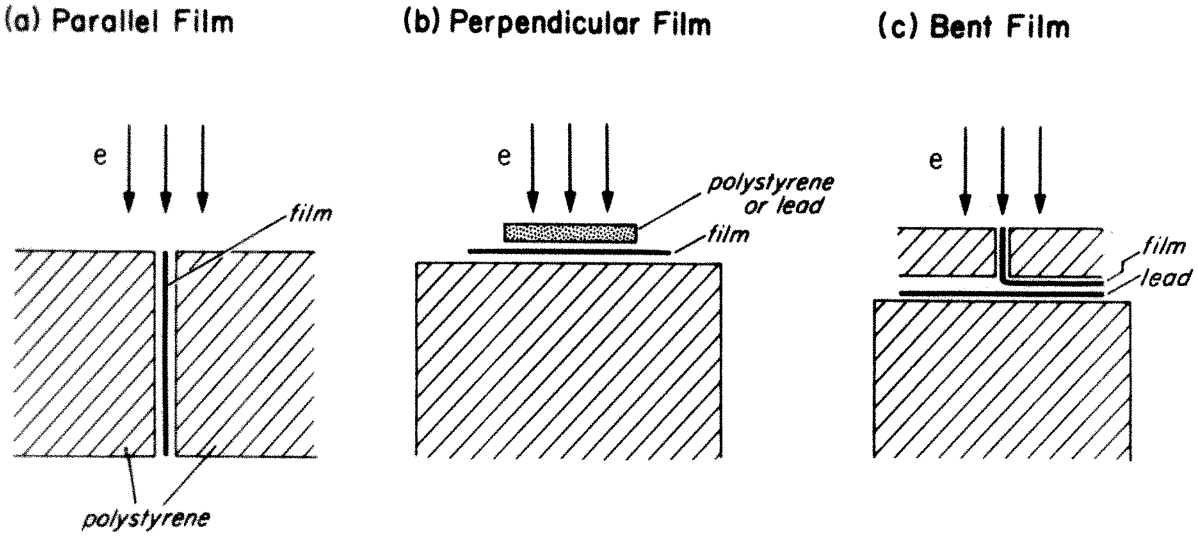

FIG. 2.
Diagrams illustrating film position with respect to beam axis.

lead is too thin the surface dose may even be enhanced. For example, if 1 mm thick lead sheet is used for external shielding in a 13 MeV beam, the surface dose behind the lead is increased by 20 per cent relative to the peak dose for the unshielded condition.

The X-ray contamination is slightly increased when using lead shields due to the bremsstrahlung interactions. This can be seen by comparing tail ends of the curves in Figs. 1 and 3. However, in treating small volumes this increase in X-ray contamination is not of much concern.

2. Effect of blocking on dose-rate. Blocking a portion of the electron beam field does not significantly alter the dose rate in the open portion of the field, provided the area of the open portion is not too small. Measurements indicated that blocking a 10 cm diameter cone to give a field 2 cm diameter did not change the dose rate. However, when the field was reduced further to 1 cm diameter the dose rate dropped steeply to 85 per cent of the open field value. Thus, if a field produced by a lead cut-out is smaller than the minimum size required for maximum lateral dose build-up, a special output calibration is necessary for that field.

Internal Shielding

1. Electron back-scatter (EBS). One of the problems in using lead for internal shielding is the increased back-scatter of electrons (EBS) from lead compared to soft tissue. This has been discussed by Okumura

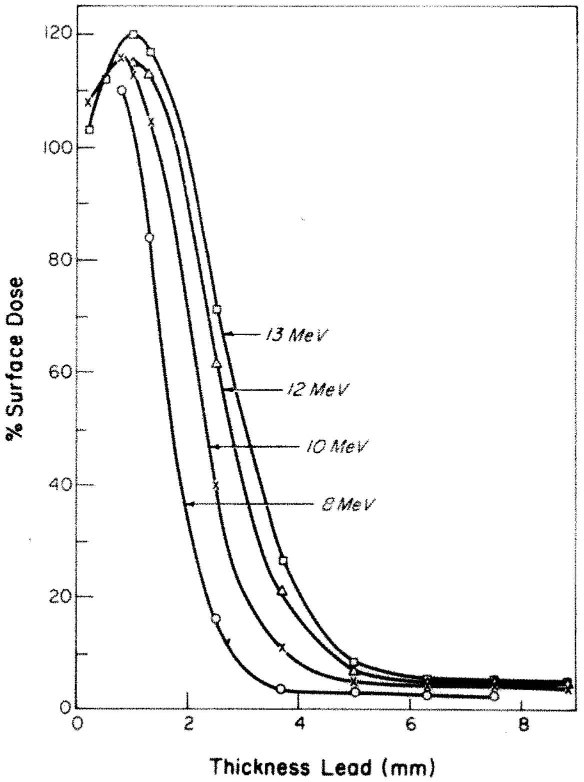

FIG. 3.
Phantom surface dose versus lead thickness as a percentage of the peak dose in phantom without lead. Cone size, 6 cm diameter.

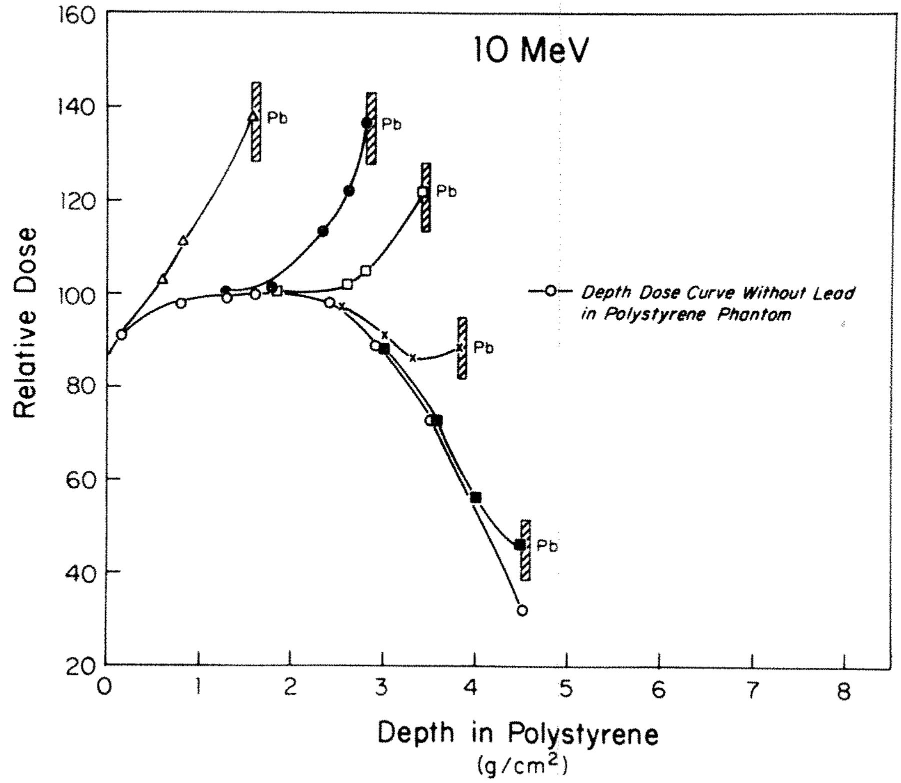

Fig. 4.
Modification of depth dose by lead placed at various depths in the phantom. Lead thickness = 1·7 mm.

et al., (1971), and Saunders and Peters (1974). The EBS is analysed here to study the effect in the range 8–13 MeV.

The thickness of lead used in these measurements was 1·7 mm. The minimum thickness of lead required to give full EBS was found to be about 1·0 mm at 10 MeV. As seen in Fig. 4, the dose at the lead interface decreases with depth. However, the percentage increase in dose at the interface relative to the dose expected at the same point in a homogeneous polystyrene phantom does not change significantly with depth. The range of EBS is about 1 cm, measured from the interface back toward the phantom surface.

Figure 5 gives the effect of energy on the amount and range of EBS. It is seen that although the percentage increase in EBS decreases with energy, the change is not substantial in the energy range studied. It may be noted that the magnitude of the increase in dose at the lead/polystyrene interface is 40 to 50 per cent depending on energy and depth. This differs

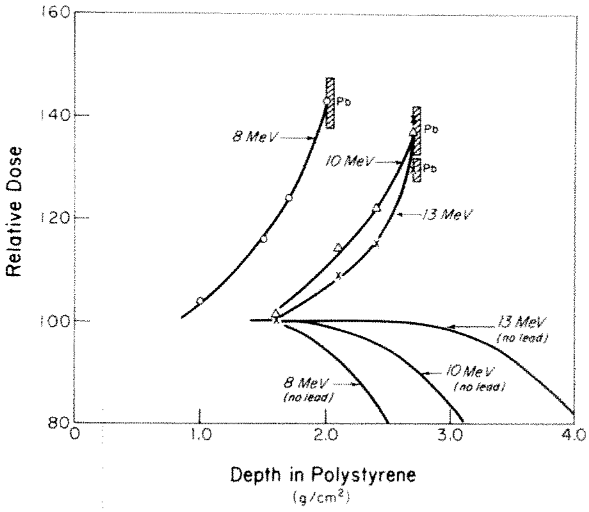

Fig. 5.
Modification of depth dose by lead for different energies. The lead was placed just beyond the region of peak dose in each case.

significantly from the figures of Saunders and Peters (1974) who found a 68 per cent increase in dose at an interface depth of 2 cm with 7·7 MeV incident energy.

In clinical applications for the energy range discussed, 5 to 10 mm of tissue equivalent bolus may be placed between the internal shield and the preceding tissue surface to avoid excessive dose near the interface. Alternatively, it has been suggested that the lead should be sheathed with 2 mm of aluminium (Saunders and Peters, 1974).

2. *Lead Clay for Internal Shielding*. For internal shielding in the range of 8–13 MeV, about 2 mm lead placed beyond the region of peak dose in the tissue medium would be adequate. However, a lead sheet placed internally, such as for intra-oral shielding, may cause discomfort to the patient. A flexible lead clay* in this case would be advantageous. Because of the toxicity of the elemental lead in the lead clay, it should be wrapped in a thin plastic foil. The lead clay has a density of 4·5 g/cm^3 and can be rolled into sheets of uniform thickness. Transmission measurements with the lead clay showed that it is 40 per cent as effective as lead in electron beam shielding. Thus, for internal shielding a 5 mm thick sheet of lead clay is adequate. EBS properties of lead clay are similar to those of the pure lead.

CONCLUSIONS

It has been shown that if thin lead is used in electron beam shielding it may enhance rather than reduce the surface dose. A thickness of lead equivalent to the maximum range of the electrons would reduce the transmitted dose to a practical minimum.

Secondary blocking does not alter the dose rate in the open portion of the field, provided full lateral build-up of dose is achieved.

Lead shields used internally cause a significant back-scattering of electrons. In the range 8–13 MeV, this may result in a 40–50 per cent increase in dose at the interface. About 1·0 cm of tissue equivalent bolus between the lead and the tissue surface is required to dissipate this effect.

A lead clay, because of its flexibility, offers an advantage over lead for internal shielding. In electron beam absorption the lead clay is 40 per cent as effective as lead.

ACKNOWLEDGMENTS

We wish to thank Howard Larson, Peggy Maas and Georgia Thompson for their assistance in this work.

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*Manufactured by Reactor Experiment, Inc., San Carlos, California.

Book review

Integrated Atlas of Gastric Diseases. By Klaus Krentz, pp. viii+203, 1976 (Stuttgart, Georg Thieme Publishers), DM.120.

This book attempts to combine X-ray appearances with endoscopic findings. A short clinical history and some laboratory findings are included with each case. The endoscopic reproductions are good. Unfortunately, little else can be said in favour of this book. The references are in most cases old and the text, which was originally written in German and has been translated into English by Dr. Heinrich Lamm, is quaint and extremely difficult to understand. Expressions such as "gotten trapped" and descriptive phrases such as "scarry changes", "fine bloody suggillations" and "greyish smearing" are, to say the least, unusual in medical texts. It would have been preferable if this book had not been translated.

J. A. GLEESON.

1976, *British Journal of Radiology*, *49*, 887–888 OCTOBER 1976

Technical notes

A technique for cranial-spinal irradiation

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(*Received March 1976*)

Accurate and homogenous irradiation of junctions between irradiated tissue volumes is a persistent problem in radiation oncology. The treatment of medulloblastomas and other tumours requiring irradiation of the entire central nervous system presents a particularly difficult junctional problem. Several solutions have been proposed, each with its own inherent advantages and disadvantages. The two solutions in most widespread use involve either shifting the level of abutting ports over the cervical spine, or calculating a gap between the brain and spinal fields in the same region. The purpose of this note is to present a method of joining cranial and spinal treatment volumes which provides a reproducibly uniform dose distribution across the junction at a specified depth.

To ensure dose homogeneity, we prefer to irradiate the brain through parallel opposed lateral treatment ports. Joining these with a posterior port over the spinal cord presents a three-beam junctional problem with beam incidence at 90 deg. angles. Our proposed solution involves a 6 cm overlap of treatment volumes with lead spoilers inserted in the edge of the beams corresponding to the region of overlap (Fig. 1).

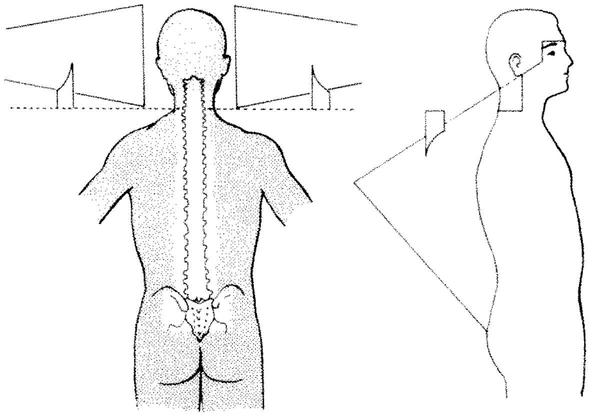

FIG. 1.

Diagram of treatment fields illustrating the overlapping junction and the position of the spoilers. The spinal cord could be irradiated through two posterior ports in larger patients.

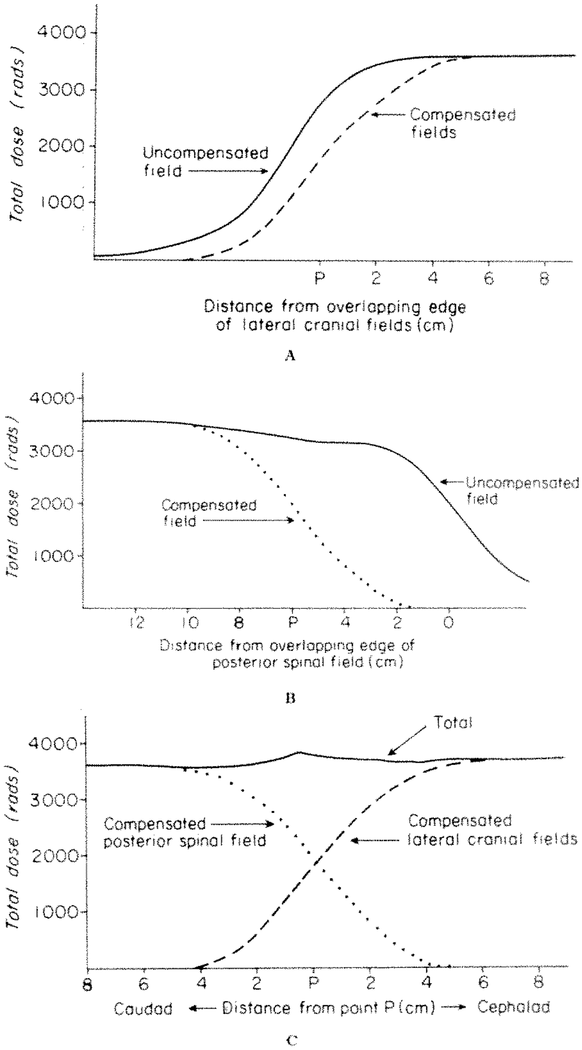

FIG. 2.

(A) Dose distributions of the cranial fields at midline in the region of the junction, with and without the compensating effect of the spoilers. Point P is a reference point on the graph representing the caudad edge of the cranial fields.

(B) Dose distributions of the spinal field at depth in the region of the junction with and without the compensating effect of the spoiler.

(C) Total dose distribution in the region of the junction illustrating the contribution of compensated cranial and spinal fields.

1976, *British Journal of Radiology*, *49*, 888–891

The spoilers are designed to attentuate the overlapping edge of each beam so that the summed dose delivered to the cervical spinal cord across the region of overlap is constant and equal to the dose delivered to the remainder of the central nervous system. To accomplish this, the patient's brain and spinal cord are localized, and treatment ports are arranged as in Fig. 1. Then a sagittal contour of the spine and a coronal contour of the head and neck are obtained. With this information, the dose distribution within the target volume of each uncompensated treatment field can be determined by computer dosimetry. The overlapping portion of each field must then be differentially attenuated so that when the dose at corresponding points from the lateral and posterior fields are added together, a constant dose distribution at the desired depth results. The shapes of the spoilers are determined by calculating the thickness of lead at 5 mm intervals necessary to produce the required attenuation. A single spoiler may be used for the parallel opposed cranial beams, but a second one must be designed for the posterior spinal beam.

To illustrate this technique, data from a medulloblastoma treatment plan is presented in Fig. 2. We planned to deliver 3,600 rad to the entire brain and spinal axis, to be followed by a 1,400 rad boost to the brain. A Picker C8M/80 ^{60}Co therapy machine was used.

DISCUSSION

While carefully applied alternative methods yield adequate results, this technique has two advantages over others currently in widespread use. Methods which involve shifting the level of abutting ports over the cervical spine introduce a volume of high dose inhomogeneity due to beam divergence (Jones, 1976). As demonstrated in Fig. 2, this is practically eliminated by the use of spoilers with overlapping fields. Techniques involving gap calculations require a high degree of reproducible precision with each daily setup, and an error of several millimetres on the skin can produce marked variations in the depth dose. A 4 mm error in the gap on the skin can produce, depending on beam energy and collimation, up to a 100 per cent variation in dose at depth (Armstrong and Tait, 1973). Owing to the gradual attentuation induced by the spoilers, this same error in set-up results in a 10 per cent dose variation at depth with this method.

These advantages make this technique an attractive alternative to other popular solutions to this junctional problem, and are worth the initial extra effort required in the construction of the spoilers.

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A toe monitor system for cerebro-femoral catheterizations

By M. Ahmon, B.Sc., S. H. Dallas, M.A., M.B., B.Chir., F.F.A.R.C.S., D.A., and J. H.W. Pexman, M.B., Ch.B., D.M.R.D., F.R.C.R.*

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(*Received April 1976*)

One of the complications of catheterizations of the femoral artery for cerebral angiography is occlusion of this artery at the puncture site or the production of distal emboli and Jacobsson *et al.*, (1969) quote the incidence of these as 0.2% to 8% with an amputation rate of between 0.003% to 0.0002%. One of the ways of reducing femoral artery morbidity is by monitoring the pulse distal to the puncture site.

The technique of photople-thysmography has been known for over 30 years (Evans, 1944; Brown, 1967; Weinman, 1967, 1972) and although not widely accepted as a quantitative measure of blood pressure or volume, the method is useful when it is required to know the relative volume of blood present at any given time. We have used this technique to monitor peripheral circulation in the catheterized leg, using the non-catheterized leg as a control and our preliminary results indicate the value of this technique.

APPARATUS AND TECHNIQUE

The principle exploits the fact that living tissues are translucent to light, particularly in the infra red region, whereas blood is opaque. Two modes of operation are commonly used – transmitted light or reflected light. In the transmitted light mode as used by us, a photodetector and light source are placed opposite each other with the tissue sandwiched in between.

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*At present with Prince Henry Hospital, Sydney, Australia

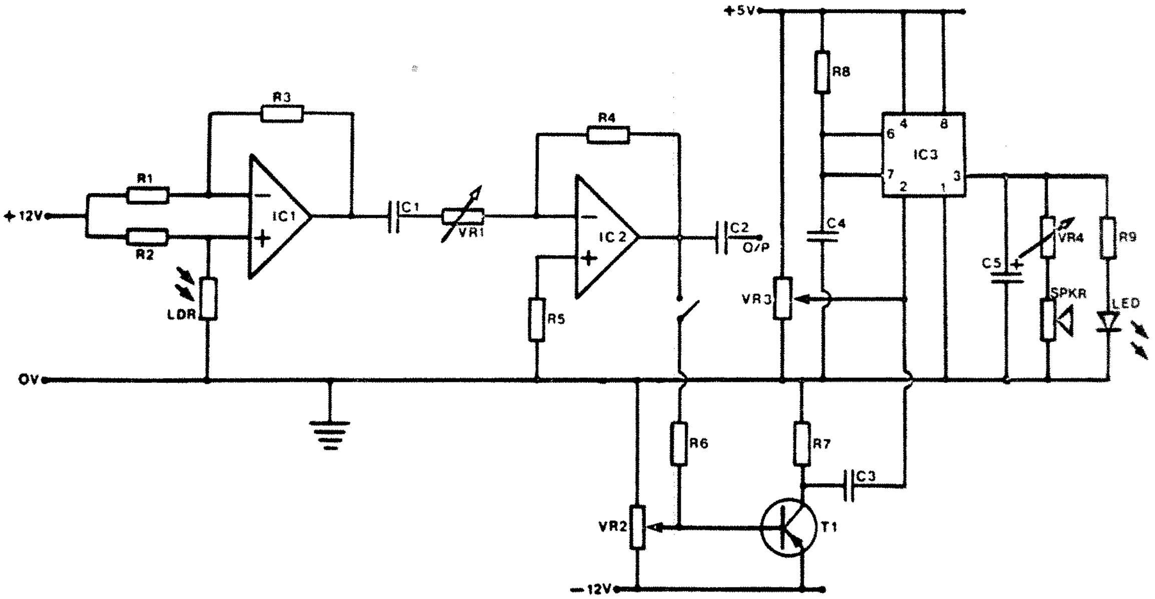

FIG. 1.
Circuit diagram of one channel of monitor, shown with audio–visual stage.

The transducers of the system were specially fabricated from aluminium and Perspex. This was made in two sections, one-half containing a photoresistor (LDR) and the other half containing two lamps wired in parallel, each drawing a current of 40–50 mA. The toe to be monitored is sandwiched between these two sections which are then held together with velcro. The lamps are not in direct contact with the skin and heat from the lamps is dissipated in the aluminium block.

The photoresistor forms one arm of an unbalanced Wheatstone bridge (Fig. 1). Since blood volume changes in the toes could be quite small in relation to other parts of the body, the more sensitive full bridge has to be used instead of a simpler half bridge. Any change in the bridge is detected by the operational amplifier (ICI) which is connected in the differential input mode with another arm of the bridge (R_3) as its feedback element. Advantages of this circuit are that the bridge supply is earthed and the output is independent of the bridge impedance levels. One drawback is that amplification is not provided and an additional stage (IC2) had to be used to boost the pulses up to an acceptable level required by the chart recorder. In addition, an audio-visual output was required. A monostable stage was constructed using an integrated circuit timer chip (IC3) fired by an adjustable trigger. This timer chip is capable of producing output currents of up to 200 mA and is used to drive an audible alarm unit (SPKR) and a light emitting diode (LED). The audio-visual stage can be switched off but may be useful during X-ray screening with dimmed lighting.

The power supply to the bridge is provided by a stabilized 12 V line. A separate voltage line is used to power the tungsten lamps in the transducers. For optimum results the lamp current should be adjusted for each patient, depending on thickness of the toe and volume of blood pulse, to give equal pulse amplitudes on the chart recorder.

A transducer is placed on each big toe and the output signals are connected to a two-channel chart recorder which has a variable speed but which we run at 50 mm/min.

After the patient is anaesthetized, the two transducers are applied and adjusted so that there is an equal deflection on the recorder from each toe. Various factors vary the amplitude throughout the procedure but these affect both sides equally. Any reduction in the circulation of the artery being cannulated is therefore immediately apparent as a difference in amplitude of the two pulse deflections.

The factors varying the amplitude of both channels are:

(a) Temperature. As the toes warm up the amplitude of deflection increases (and presumably cooling would decrease it correspondingly).

(b) Ventilation. Hyperventilation which we regard as important for good angiography causes a steady diminution in peripheral blood flow.

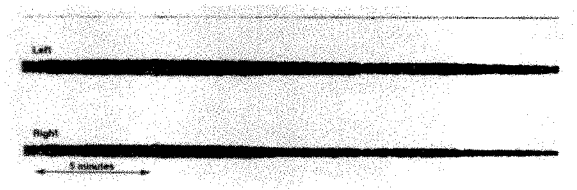

Fig. 2.
Recording from both big toes after 40 minutes from start of anaesthetic with hyperventilation, and 30 minutes from catheterization of right femoral artery (the lower tracing).

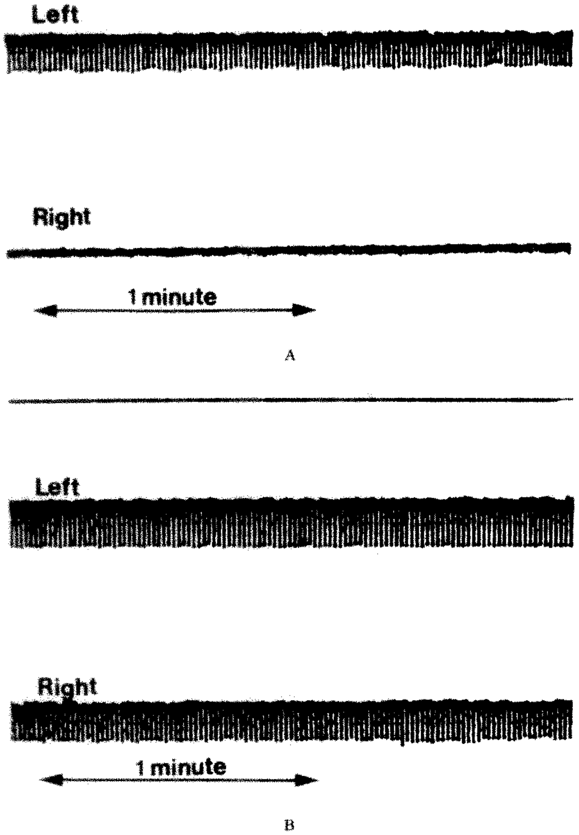

Fig. 3.
(A) Shows the catheterized leg (lower tracing) has very diminished toe pulsation after 90 minutes of hyperventilation, whilst (B) shows not such a marked difference with normocapnoea, two hours after catheterization. (N.B. the lower trace must only be compared to its own control).

(c) Movement of the drapes. This causes less disturbance with transducers specifically designed for toes but is usually seen as an equal change in amplitude.

The apparatus has so far been used on 15 cases.

Preliminary Results

Rather surprisingly only three tracings were regarded as completely normal. All the others, with two exceptions, showed bilateral diminution in amplitude due to hyperventilation with slightly more reduction on the cannulated side (Fig. 2). If the diminution became very marked termination of the examination was expedited. The two exceptions were on a patient who was examined twice for selective spinal angiography. Under hyperventilation marked reduction in blood flow in the catheterized leg made us abandon the examination after 1½ hours. However, it was subsequently successfully repeated taking two hours with ventilation to produce normocapnoea (Fig. 3).

On the first occasion, this patient's peripheral blood supply had returned to normal two hours after the examination when tested on the ward with our monitor.

In one very obese patient in whom the femoral arteries could not be palpated, detection and subsequent cannulation of the femoral artery was successfully achieved by watching the pulse trace to detect the artery with the cannula and needle.

Discussion

Impairment of peripheral circulation after femoral puncture for cerebral catheterization is usually not discovered until the end of the procedure, and to prevent thrombo-embolism occurring an early warning monitoring system is desirable so that steps can be taken to modify or abandon the procedure if necessary.

Standard pulse meters are unsatisfacory as they are designed for fingers and are unreliable on toes—particularly on cold toes on which they give no reading at all! The least movement of the surgical drapes covering the toe could give a false impression of occlusion. Hence there was a need for a purpose built monitor, and it is essential to use the patient's other leg as a physiological control because temperature, movement of drapes and the patients blood pressure and arterial PCO_2 together with electrical unbalance of the apparatus altered the readings.

Although controlled hyperventilation had advantages in studying the cerebral circulation, if catheter techniques replace direct puncture ones, the value of hyperventilation must be weighted against any possible risk of increasing the likelihood of thrombo-embolism in the catheterized leg.

Patients undergoing spinal angiography, which is a very lengthy procedure should not be hyperventilated.

The apparatus can be used on the wards after the procedure to monitor any limb in which the peripheral circulation following femoral catheterization gives rise for concern.

ACKNOWLEDGMENTS

We wish to thank the medical and para-medical staff of the X-ray and Medical Physics Departments for their help, and especially Mrs. Margaret Purvis for the preparation of the manuscript.

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Book review

Report of an IAEA/WHO seminar on afterloading techniques in radiotherapy (particularly related to the treatment of cancer of the uterus), pp. 137, 1975, available free on application to The World Health Organization.

This is an interesting, well-written and comprehensive report dealing essentially with the treatment of cancer of the uterus by radiotherapy and the extension of such services in developing countries.

The main report, consisting of ten chapters (52 pages), is supplemented by a number of annexes written by individual authors and intended to provide additional information on particular aspects of the subject.

The report deals with the disease and its treatment, using simple manual afterloading or more sophisticated remote afterloading. It makes recommendations regarding the organization of treatment services on a world-wide basis. Physical, radiobiological and socioeconomic factors are discussed in terms which are easily understood.

The annexes contain a miscellaneous collection of papers. My attention was particularly attracted by the ones which dealt with cancer incidence in various countries, afterloading in the U.S.S.R., a short excellent paper by Cohen on the choice of substitutes for radium, and to pages 107 and 108, which unfortunately were missing from my copy.

This report will be useful to any group who are considering introducing afterloading systems in their clinic. Annex A, which is an extract of the report of the previous meeting of the working party, contains a wealth of information on the various systems which are available and this will be supplemented by Annex C of the present report which will be issued separately and which should be most valuable when it becomes available.

The bibliography should include more references to important papers which have been published in the last few years. Although high dose-rate after-loading has been used for ten years, there is little reference to the important clinical results obtained with this technique.

There appear to be one or two misprints on page 39, where, for example, it is stated that theatre staff using preloaded applicators have received doses as high as 80 man-rem/application of 67 mg of radium. This statement is attributed to Merkas (1975), but unfortunately the appropriate reference does not appear in the bibliography. To receive such a dose many men would need to be a few centimetres from the source during the insertion. Clearly the prefix "milli" has been inadvertently excluded from either the man or the rem.

Despite these minor criticisms, the report is a valuable document which should be read by all those interested in treating cancer of the uterus in either developed or developing countries.

W. E. LIVERSAGE.

1976, *British Journal of Radiology*, *49*, 892

Case reports

Pneumothorax complicating pelvic pneumography

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(*Received January, 1976*)

Isolated cases of pneumothorax or pneumomediastinum have been reported following therapeutic pneumoperitoneum (Stein, 1951) and of course diagnostic pneumoperitoneum may be used to prove a suspected defect in the diaphragm, but the following is believed to be the first case reported of pneumothorax complicating pelvic pneumography.

CASE REPORT

A 36-year-old woman was referred for pelvic pneumography because of pelvic pain and suspicion of a right adnexal mass. Following local anaesthesia, an 18-gauge spinal needle was introduced through the anterior abdominal wall 2 cm to the left of and above the umbilicus. 1,400 cm^2 of nitrous oxide were instilled through the needle without difficulty. The needle was withdrawn and the patient turned to the prone position and tipped to 45 deg. Trendelenburg. She then began to cough and complained of mild dyspnoea. Standard films of the pelvis were obtained. Upon resumption of the supine position, the abdomen appeared flat. Review of the films revealed very little air within the peritoneal cavity. A supine film of the chest demonstrated a small-pneumothorax (Fig. 1). Resumption of the steep Trendelenburg position did not affect the amount of air within the thorax. The patient was observed closely over the next hour. Her mild symptoms abated. A repeat film of the chest at that time revealed nearly complete disappearance of the pneumothorax. She was allowed to return home.

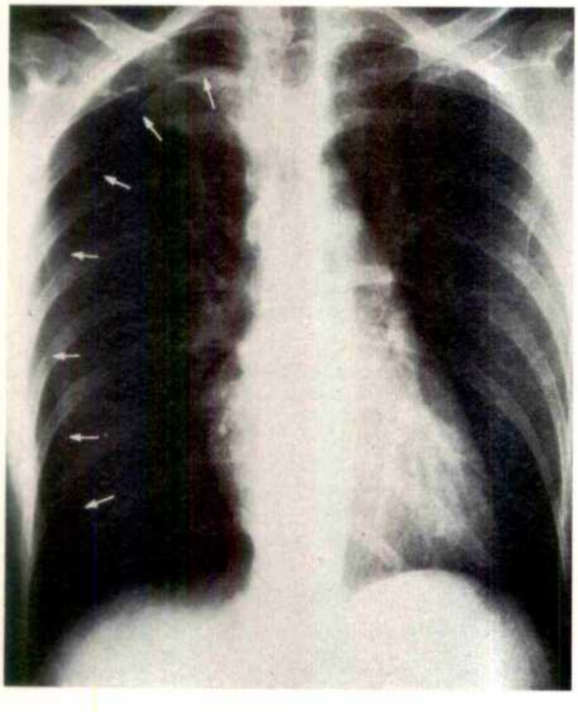

FIG. 1.

Supine antero-posterior view of the chest. Note the pneumothorax (arrows).

DISCUSSION

Stein (1951) collected 24 cases of spontaneous pneumothorax following pneumoperitoneum, mostly for therapeutic purposes. Nearly all were right sided. There were two fatalities (Yannitelli *et al.*, 1949; Smith, 1943). Although some have postulated that the air from the peritoneal cavity forces its way through the natural diaphragmatic openings, the more likely explanation is that the air passes through a congenital defect in the diaphragm. The autopsied cases support the latter view (Yannitelli *et al.*, 1949; Smith, 1943). Most of these congenital defects are posterolateral in location (foramen of Bochdalek).

This young healthy patient had mild respiratory symptoms as a result of the small pneumothorax. Because nitrous oxide was used, it was resorbed in one hour. If a similar complication developed in a patient with borderline respiratory function, extreme dyspnoea and cyanosis might occur. In that event, needle aspiration of the intrathoracic gas should provide definite therapy.

An additional lesson of the case is that one should carefully monitor the amount of induced nitrous oxide in performing pneumoperitonography lest large amounts of gas pass unnoticed through a diaphragmatic defect to collapse a lung.

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Address for reprints: Department of Radiology, Sequoia Hospital, Redwood City, California 94062, U.S.A.

1976, *British Journal of Radiology*, *49*, 893–894

Case reports

A soft tissue sarcoma occurring four years after radiotherapy

By S. K. The, M.D., M. M. Qasim, M.B., B.S., D.T.M.H., D.M.R.T., F.R.C.R., and A. Talerman, M.D., M.R.C. Path.*

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Received March, 1976 and in revised form May, 1976)

One of the most serious adverse effects of radiotherapy is the induction of neoplasia in the tissues subjected to treatment. In spite of the very wide use of radiotherapy in the treatment of malignant disease, such induced neoplasms are not common and soft tissue sarcomas are rare (Gane *et al.*, 1970; Jones 1953; Seydel 1975). We report a case of fibrosarcoma arising in the radiation field four years after successful radiotherapy for bronchial carcinoma.

CASE REPORT

In February 1970 the patient, a 50-year-old male, complained of dyspnoea and pain in the chest after an attack of influenza. He had smoked 15 cigarettes a day for 35 years, but otherwise his past history was unremarkable. A chest X ray in April 1970 showed evidence of emphysema and irregular shadowing in the right hilar region, and sputum cytology revealed atypical squamous cells. Bronchoscopy showed narrowing of the right main bronchus near its origin and a keratinising squamous cell carcinoma was found at biopsy. The tumour was inoperable and radiotherapy was given to the lesion and surrounding mediastinal structures with two parallel opposed fields of 14 × 12 cm using a 4 MeV linear accelerator. A tumour dose of 5400 R was given in a split course, ten fractions of 300 R each given over two weeks being followed by a rest period of three weeks and then a further eight fractions of 300 R each. The overall duration of treatment was 59 days. At the end of this treatment in August 1970 the tumour was no longer visible radiologically and the patient had no symptoms.

The patient remained well, although subcutaneous fibrosis was noted in the field of irradiation. In March 1974 the fibrosis in the posterior field was found to be more severe than in other areas and this progressed to induration and ulceration (Fig. 1). Towards the end of 1974 multiple small skin nodules were present and biopsy of one of these revealed a poorly differentiated malignant connective tissue tumour composed of spindle shaped, fusiform and oval cells showing marked cellular and nuclear pleomorphism, giant cells, brisk mitotic activity and abnormal mitoses (Fig. 2). The tumour cells were surrounded by reticulin fibres (Fig. 3) and reached the immediate vicinity of blood vessel walls confirming the diagnosis of a poorly differentiated fibrosarcoma.

In February 1975 the skin nodules became larger (Fig. 4) and lymph nodes were present in both axillae and supraclavicular regions. The chest X ray taken at this time was normal. The patient's condition deteriorated; in spite of treatment by various combinations of cytotoxic agents, the skin lesion on the back and the lymph nodes continued to increase in size and he died in April 1975. Necropsy revealed extensive involvement of the subcutaneous tissues of the back by the tumour which penetrated through the chest wall and affected the pleura. There were metastatic tumour deposits in both lungs and in the mediastinal lymph nodes together with pleurisy and bronchopneumonia. There was fibrosis as well as tumour deposits in the region of the major bronchi and blood vessels. Metastatic deposits were present in the cervical, axillary, para-aortic and mesenteric lymph nodes, the liver and the thoracic vertebrae. Histologically the tumour from all the sites, including numerous sections taken from deposits present in the region of the major bronchi, the site of the tumour diagnosed in 1970, showed a poorly differentiated fibrosarcoma similar to that observed in the biopsy taken from the skin nodule (Figs. 2 and 3). Tumour deposits were present in the lumen of the blood vessels and lymphatic invasion was also present.

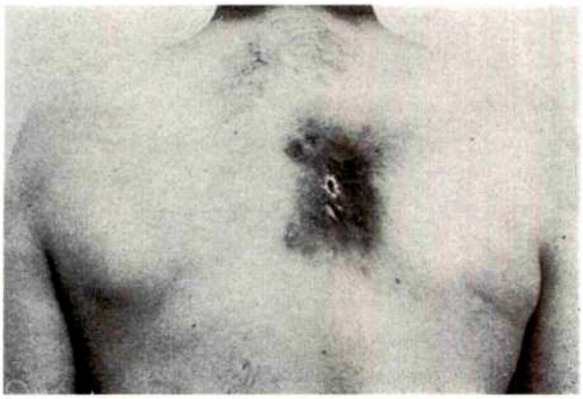

FIG. 1.

The induration and focal ulceration affecting the posterior radiation field in September 1974.

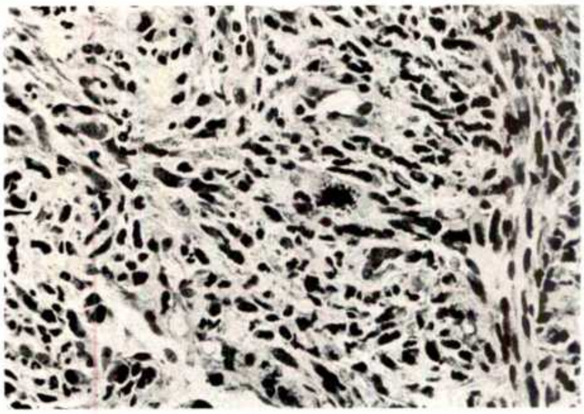

FIG. 2.

The microscopic appearance of the tumour arising in the posterior radiation field showing poorly differentiated fibrosarcoma. (H & E × 380).

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*Address for correspondence: Dr. A. Talerman, Department of Pathology, Institute of Radiotherapy, Postbus 5201, Rotterdam, Holland.

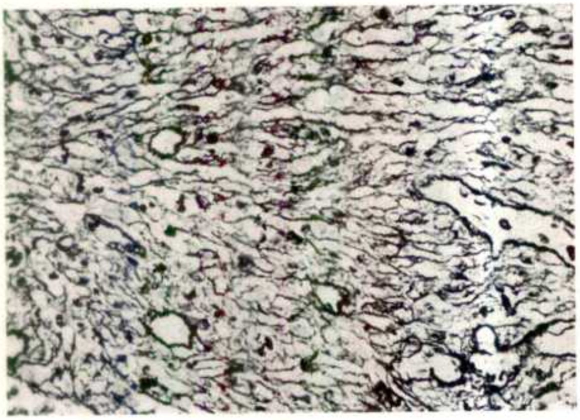

FIG. 3.
The microscopic appearance of the tumour arising in the back showing marked production of reticulin fibres typical of a connective tissue tumour. (Gomori's reticulin × 235).

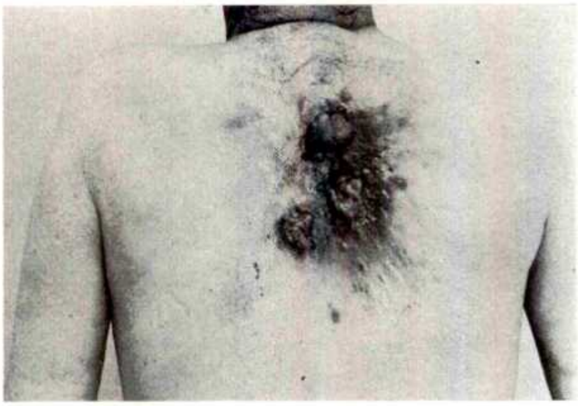

FIG. 4.
The appearance of the tumour arising in the indurated area in the posterior radiation field in February 1975.

DISCUSSION

The literature dealing with the development of sarcoma in subcutaneous tissue after irradiation has been reviewed by Jones (1953). Most of the reported cases occurred as a late complication of radiation therapy for lupus vulgaris and other benign conditions. The histological diagnosis in a number of these patients is open to question and only a few cases have been reported since squamous call carcinoma exhibiting a spindle cell pattern has been recognised. Four cases of radiation induced fibrosarcoma were mentioned by Stout (1948), but the first well documented case was that described by Jones in 1953, a fibrosarcoma developing in subcutaneous tissue in the sacral area seven years after radiotherapy for a carcinoma of the bladder. Since then only a few further cases have been reported (Gane *et al.*, 1970; Sagerman *et al.*, 1969; Saydel 1975; Soloway 1966).

The latent period between radiotherapy and the development of a fibrosarcoma ranged between three and 38 years (Gane *et al.*, 1970). No previous cases have been reported after treatment for a carcinoma of the bronchus because of the poor survival rate.

In the treatment of radiation induced fibrosarcoma, radiotherapy (Gane *et al.*, 1970), and in this patient chemotherapy, have had no effect on the course of the disease, but early complete excision of the tumour has resulted in a complete cure in some cases (Gane *et al.*, 1970; Jones 1953). The use of beams with increased penetration in modern X ray machines has led to decreased skin damage but the amount of radiation to the subcutaneous tissues is increased. Therefore, it is possible, that radiation induced soft tissue sarcoma may be seen more frequently in the future.

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1976, *British Journal of Radiology*, *49*, 895–896

Short communications

Ultrasonic grey-scale recording with rapid processing film

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(*Received May, 1976*)

With the advent of grey scaling in ultrasonic diagnosis, one problem is recording the enhanced image on the TV monitor. Polaroid film, type 107C, which produces prints within 45 seconds is convenient but can only cope with a limited tonal range in the image being photographed. Increased latitude is obtainable with transparencies, but small films present difficulties in handling, processing, filing and in recording patient data.

It is suggested that in an X-ray department equipped with rapid processing a convenient method is to use a special film cassette attachment (Picker type M1–7203 Model 810) for a Polaroid camera with a flat pack back. This attachment accepts a 10 × 8 in. film. Patient data is added by a conventional darkroom film marker. Up to six images can be recorded on one film.

A comparison made of the various types of Kodak RP film (RP/D, RP/L, RP/M, RP/SU, RP/X) suggests that type RP/SU (subtraction) film is the most suitable (Fig. 1). This film accepts a wide tonal range, is of adequate speed, and has a fine grain. With the latitude of this film camera settings are less critical than with the type 107C film. Ten different grey tones can be discerned, against approximately seven for Polaroid film. The cost is about 36p, which with six exposures per film is considerably cheaper than Polaroid prints at 18p per exposure.

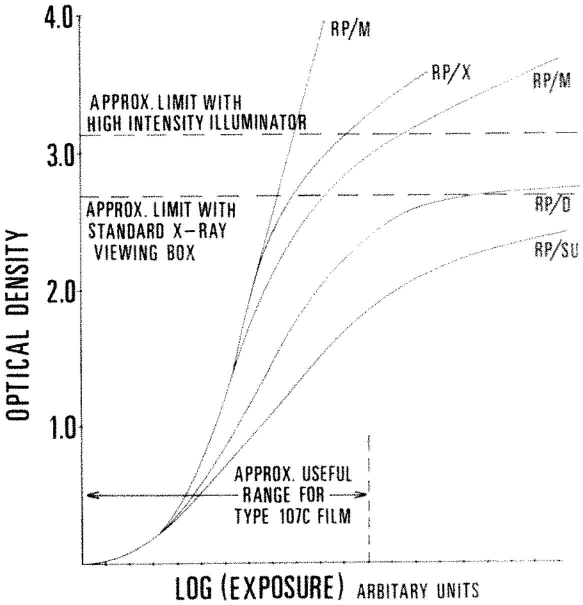

FIG. 1

Potentiation of radiation myelitis in rats by hyperthermia

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(*Received April, 1976*)

With the recent revival of interest in hyperthermia as an anti-tumour modality (Henderson and Pettigrew, 1971), there is still relatively little information published regarding the interaction of hyperthermia with radiation on normal tissues (Crile, 1963; Robinson *et al.*, 1974). Such information on biological effects is needed, particularly in respect of late effects in organs such as lung, kidney and nervous tissue.

In our experiments, Fischer 344 female rats weighing approximately 150 g were treated with single doses of radiation (4 MeV photons) to a 2.5 cm segment of spinal cord with the cephalad border at the anti-clinal vertebrae. Animals were anaesthetized with intraperitoneal injections of sodium pentobarbital (25 mg/kg), and 15 animals were treated at each radiation dose point. The animals receiving radiation alone were given doses of 2000, 2300, 2600 or 2900 rad at a dose-rate of 300 rad per min. The radiation groups receiving heat treatment in addition were given single doses of 1000, 1500, 2000 or 2600 rad which was then immediately followed by whole-body hyperthermic treatment of anaesthetized animals to 42°C for 30 min. Hyperthermia was produced by placing the animals in chambers heated with warm moist air. Rectal temperature was monitored to keep the animals at constant temperature. Spinal canal temperature was monitored in other animals by surgical placement of a thermistor into the spinal canal. Spinal canal temperatures paralleled rectal temperatures to within 0.2°C before, during, and after the period of hyperthermic treatment.

As expected (Van der Kogel and Barendsen, 1974; Leith *et al.*, 1975), the threshold dose for production of myelopathy after single doses of radiation was about 2000 rad: only one of ten rats receiving this dose of radiation alone showed paralysis at ten months after irradiation. At eight months after irradiation 12 of 13 rats irradiated with 2300 rad showed paralysis, while at the 2600 and 2900 rad dose levels 100% of exposed animals showed paralysis.

The striking findings however occurred in the rats receiving 2000 rad plus the 42°C treatment for 30 minutes. At seven months post irradiation five of nine surviving animals showed overt myelopathy (several animals were lost due to renal radiation damage or severe respiratory infections before showing neurological changes). Thus far no myelopathy has been seen up to nine months post-irradiation in the rats receiving 1000 or 1500 rad plus heat treatment. In the rats receiving 2600 rad plus heat treatment, ten of ten animals are paralysed. Further studies are being performed at different radiation doses to confirm these findings and further define the possible change in the threshold dose for production of myelopathy in animals receiving the combined modality treatment. There appears to be no significant difference in the latent period before onset of symptomology between the two types of treatment conditions.

We feel that the production of paralysis in over 50% of rats receiving 2000 rad plus hyperthermia is a significant finding, particularly in view of the fact that 2000 rad of photons alone produces virtually no functional impairment. If this is confirmed by further work it will have very important clinical implications for situations in which a portion of the spinal cord may be in the radiation field (as, for example, in the treatment of Hodgkin's disease or lung cancer). We feel that it is crucial for anyone doing clinical trials with combined hyperthermia and radiation to realize that radiation tolerance of the spinal cord may be greatly altered by hyperthermia.

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1976, *British Journal of Radiology*, *49*, 897–898 OCTOBER 1976

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

SENSITIVITY OF TDF AND CRE TO VARIATIONS IN EXPONENTS OF N AND T

In a recent letter, Supe *et al.* (1976) showed, quite correctly, that TDFs (Orton and Ellis, 1973) are more sensitive to variations in the exponents of N and T (in the basic NSD equation) than are CREs (Kirk *et al.*, 1971). They also quoted experimental data, which showed that the specific values of these exponents are not known precisely and are subject to considerable debate. They concluded that the "... use of TDF is not to be advocated at the present juncture because of its greater dependence on variations in the exponents of T and N", and that CRE is therefore more reliable.

This conclusion intrigued me, since it had always been my contention that the TDF and CRE equations were simply different formulations of the same concept (*viz.* NSD), and hence were fundamentally identical. Two questions arose in my mind.

(1) Since, in practical application, CREs and TDFs are simply numbers used for equating or comparing treatment régimes, is this apparent difference in sensitivity to the values of the exponents significant in "clinical practice"?

(2) How important are changes in the exponents when the concepts are used?

The answers to these questions follow.

1. *Practical difference between CRE and TDF*

It is shown below that the solution to any practical clinical problem using CRE is identical to the solution obtained using TDF. For instance, the TDF solution to the example given in the letter of Supe *et al.* (1976), is identical to the CRE solution. However, theirs was a bad example since it involved a rest period during treatment, and Kirk *et al.* (1975) have recommended a different "gap correction factor" to that utilized by Supe *et al.* (1976). The equivalence of the CRE and TDF methods is better illustrated by the following example, in which the exponents of N and T are represented by J and H respectively.

EXAMPLE

Problem

What dose given in 20 treatments at 5 fractions per week is equivalent to 6000 rad given in 30 treatments also at 5 fractions per week?

CRE solution (Kirk *et al.*, 1971)

The planned CRE $= 200 \times 30 \times (30)^{-J} \times (40)^{-H}$

which must be equal to the new CRE

$$= d \times 20 \times (20)^{-J} \times (\tfrac{2}{3} \times 40)^{-H}$$

$$\therefore d = 200 \times \left(\frac{30}{20}\right) \times \left(\frac{30}{20}\right)^{-J} \times \left(\frac{3}{2}\right)^{-H}$$

$$= 200 \times \left(\frac{3}{2}\right)^{1-J-H}$$

TDF solution (Orton and Ellis, 1973)

The planned TDF $= (200)^{1/1-J-H} \times 30 \times (x)^{H/1-J-H} \times 10^{-3}$

which must be equal to the new TDF

$$= (\mathrm{d})^{1/1-J-H} \times 20 \times (x)^{H/1-J-H} \times 10^{-3}$$

$$\therefore (\mathrm{d})^{1/1-J-H} = (200)^{1/1-J-H} \times \left(\frac{30}{20}\right)$$

$$\therefore \mathrm{d} = 200 \times \left(\frac{3}{2}\right)^{1-J-H}$$

This is identical to the CRE solution. Hence, whatever values are chosen for J and H, the CRE method cannot be more accurate or reliable than the TDF method.

2. *How important are the exponents?*

In order to demonstrate the sensitivity of the TDF method to changes in the values of the exponents, the previous example was solved for the various combinations of J and H which were cited by Supe *et al.* (1976). These solutions are shown in Table I, in which are shown also the percent variations from the solution obtained by using the Ellis exponents of 0.24 and 0.11. Note that variations are typically less than ±3%, and that even for the drastic changes (*viz.* $J+H=0.46$) suggested by Berry *et al.* (1974), a change of less than 5% occurs in the solution.

In summary, it has been demonstrated that the CRE and TDF methods are exactly equivalent in "clinical practice". However, it should be stressed that, since CREs are not linearly additive, the TDF method greatly reduces the probability of arithmetical error, particularly when used for the analysis of more complex treatment régimes such as those involving gaps in treatment or when not all fields are treated daily. Furthermore, for the solution of typical clinical problems, *the TDF (and CRE) method is not very sensitive to changes in the exponents of* N *and* T.

I would like to conclude with a word of caution. The analysis I have presented should not be taken as approbation of the universal use of the TDF (and hence NSD) concept. The theory is only an approximate representation of a highly complex sequence of biological events occuring during a course of radiotherapy. It is based on clinical evidence obtained by retrospective analysis of typical radiotherapy data, and hence should be used with great caution if the time, dose, or fractionation differ significantly from that commonly used in conventional radiotherapeutic practice.

Yours, etc.,
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TABLE I

DOSES/FRACTION GIVEN IN 20 DAILY TREATMENTS, WHICH WILL BE EQUIVALENT TO 6000 RAD GIVEN IN 30 DAILY TREATMENTS, AS CALCULATED BY THE TDF METHOD FOR VARIOUS VALUES OF THE EXPONENTS J AND H, WHERE NSD = (TOTAL DOSE). $(N)^{-J}$. $(T)^{-H}$

J	H	Dose/fraction (rad)	Variation from $J=0.24$, $H=0.11$ (%)
0.28	0.08	259.3	−0.4
0.28	0.11	256.1	−1.6
0.28	0.14	253.0	−2.8
0.24	0.08	263.5	+1.2
0.24	0.11	260.3	0
0.24	0.14	257.2	−1.2
0.20	0.08	267.8	+2.9
0.20	0.11	264.6	+1.6
0.20	0.14	261.4	+0.4
0.28	0.05	262.4	+0.8
$J+H=0.46$		249.0	−4.3

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The Editor—Sir,

Comment on the Introduction of SI Units into the Radiological Sciences

I am in agreement with Dr. Nicholson that the becquerel is too small by a factor of 10^6. The obvious unit is the MBq or "mega-becs". Thus, instead of administering 1 mCi, we can now say, give that patient 37 mega-becs, and it will sound like he is getting a lot more for his money. Conversely, a total body absorbed dose of 100 millirad now becomes only 1 milligray which somehow sounds more innocuous. Perhaps there may be psychological advantages to the proposed changes.

Yours, etc.,
N. Goodwin.

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REFERENCE

Nicholson, J. P., 1976. The introduction of SI units into the radiological sciences. *British Journal of Radiology*, *49*, 477.

Book review

A System for Estimation of Mean Active Bone Marrow Dose. By R. E. Ellis, M. J. R. Healy, B. Schlein and T. Tucker, pp. vii + 50, 1975 (U.S. Dept. of Health, Education and Welfare Publication FDA 76–8015, Washington D.C. 20402, U.S. Government Printing Office) $1.15.

A fortunate trans-Atlantic collaboration between Professor Ellis and Dr. Healy in this country and Drs. Schlein and Tucker of the U.S. Bureau of Radiological Health has resulted in the publication of the data on which the Adrian Committee calculated the mean dose to bone marrow in diagnostic X-ray examinations a decade ago. They are now available to other investigators.

The concisely written monograph describes the method by which measurements of exposure at bone marrow sites in a realistic phantom were made and expressed as fractions of the exposure on the skin at the centre of the incident beam. These extensive data are tabulated for twelve bone marrow sites, seven radiation qualities, four source-to-skin distances, five field areas at the skin, and for three directions of irradiation—anterior, posterior and lateral. Conversion of measured exposure at a marrow site to absorbed dose is made by approximate calculations of the photoelectric contribution from the trabeculation.

The mean marrow dose is calculated by means of a computational model in which the active bone marrow distribution is divided among elements of a grid superimposed on the body in anterior, posterior and lateral views. Tables give the fraction of active marrow associated with each grid element and also the relationships to the measurement points in the skeleton. Finally, an appendix provides the detailed computer program used to calculate the mean marrow dose for any given X-ray field.

There is a useful discussion, illustrated by graphs, of the effects of the source-skin distance, radiation quality and field area on the mean marrow dose, and comparisons are made with the work of other investigators. Mainly good agreement is shown with the results of measurements made on a phantom in the U.S., but rather poor agreement with recent calculations based on a Monte Carlo Technique, a method which must inevitably employ a greatly simplified "geometrical" representation of the human skeleton.

The book is well produced with the single exception that the tops of almost all the figures in the table of exposure ratios are rather underprinted in the reviewer's copy—though the figures are discernible. The publication, however, is a valuable and welcome one, of great use to researchers investigating the mean marrow dose in diagnostic X-ray examinations.

F. W. Spiers.

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

Lumbar Discography—Diagnostic and Therapeutic Aspects and A Spinal Evening

Two meetings organized by The British Institute of Radiology to be held on the evening of October 7, 1976 at the Institute House.

Further information from the General Secretary, The British Institute of Radiology.

Autumn Meeting North of England Branch of B.I.R.

The autumn meeting of the North of England Branch of The British Institute of Radiology will be held at the Children's Hospital, Sheffield, on Saturday, October 30.

This is the Centenary year of the Children's Hospital and the staff will be presenting short papers. If anyone fails to receive a notice of this meeting by post would they please inform the General Secretary of the, The British Institute of Radiology.

British Vacuum Council Prize Award

The British Vacuum Council offers a prize of £100 for a paper based on a postgraduate research thesis in vacuum or a related topic in which vacuum science and/or engineering is of major importance. The research in question must be carried out in a laboratory in the United Kingdom.

Papers submitted as entries for the British Vacuum Council Prize must not previously have been published elsewhere. Entries for the 1976 prize must be submitted not later than November 1 to the address shown below, from which further details are available: The Secretary, British Vacuum Council, 47 Belgrave Square, London SW1X 8QX.

The Alan Nichols Memorial Lecture

The Alan Nichols Memorial Lecture entitled "Electrostatic Imaging Methods in Radiology" will this year be given by Professor J. W. Boag, D.Sc., F.Inst.P., S.I.E.E., on Thursday, November 4, 1976, at 7.00 p.m., at the Witts Lecture Theatre, Radcliffe Infirmary.

Computing Aids to Radiotherapy

A meeting organized by The British Institute of Radiology to be held on November 18, 1976 at the Institute House.

Further information from the General Secretary, The British Institute of Radiology.

A Radiobiology Work-in-Progress Meeting

To be held in the Institute House on Friday, November 19, 1976. Information from the General Secretary, The British Institute of Radiology.

Whole Body Counting and Scanning

A meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held November 24, 1976 at the Institute House. Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Proliferation Kinetics

An all-day meeting organized by the Radiobiology Committee of The British Institute of Radiology, to be held on December 4, 1976. Further information from the General Secretary, The British Institute of Radiology.

British Medical Ultrasonics Group

The Annual Meeting of the British Medical Ultrasonics Group will be held at the University of Dundee on December 20–21, 1976.

Papers will be presented on all aspects of diagnostic ultrasound and there will be an associated commercial exhibition.

Further details and registration from: The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Effects of High LET Radiations

A radiobiology meeting to be held on January 21, 1977 at the Institute House, 32 Welbeck Street, London W1M 7PG. Further information from the General Secretary.

Radiology in the European Economic Community

A joint meeting organized by the Royal Society of Medicine (Section of Radiology) and the Royal College of Radiologists, to be held at the Royal Society of Medicine, London W1, on January 21, 1977. Details from the Royal College of Radiologists, 28 Portland Place, London W1.

Radioisotope Investigations of Diseases Involving the Endocrine Organs

An all-day meeting held jointly with the Endocrinology Society and organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on February 16, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Unorthodox Approaches to Fractionation

A meeting held jointly with the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology) on February 18, 1977. Information from the General Secretary, The British Institute of Radiology.

The British Institute of Radiology Annual Congress and Scientific Exhibition

To be held on April 14–15, 1977 at the R.I.B.A., London W1. Papers presented will include the 'Silvanus Thompson Memorial Lecture" by Mr. G. N. Hounsfield, C.B.E., of EMI Central Research Laboratories.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiation Protection: An Example of Action Against Modern Hazards

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

THE MACKENZIE DAVIDSON MEMORIAL LECTURE

To be given by Dr. David Ingvar, University of Lund on May 19, 1977.

NEW HORIZONS IN INTENSIFYING SCREEN TECHNOLOGY

An all-day meeting organized by the Industry Committee of The British Institute of Radiology on May 20, 1977 at the Middlesex Hospital Medical School, London W1. Registration details and information from the General Secretary, The British Institute of Radiology.

USE OF KRYPTON GENERATORS

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Middlesex Hospital Medical School, London, W1 on June 15, 1977. Registration and details from the General Secretary.

HYPOXIC CELL SENSITIZERS IN RADIOBIOLOGY AND RADIOTHERAPY

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV INTERNATIONAL CONGRESS OF RADIOLOGY

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colegio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Obituary

Dr. T. A. Chalmers

The many friends of Dr. T. A. Chalmers will be sad to hear of his sudden death on March 7, 1976 at his home in Southport at the age of 71.

In 1927 he graduated at the University of London and went to work at the National Physical Laboratory. Soon after he joined Professor Hopwood's department at St. Bartholomew's Hospital he was awarded his Ph.D. degree.

Dr. Chalmers is well known for his work on the separation of isotopes by the Szilard-Chalmers reaction and particularly among hospital physicists for his invention of the "Clucking-hen", an instrument widely used in searching for lost radium before geiger counters became commonly available.

He was Physicist at the Liverpool Radium Institute, later the Liverpool Clinic, and Lecturer in Radiology at the University of Liverpool for 34 years until his retirement in 1970. This period spanned the second world war, and one of the resulting problems was the continuation of radiation treatment safely in spite of air raids. Dr. Chalmers solved them in a characteristically original way by setting up a radon plant in a deep underground station where he prepared clinical sources himself.

After the war he restarted the Radiology courses at Liverpool University and will be remembered by many of his past students who are now running departments in many parts of the world.

Dr. Chalmers was quick to appreciate new developments and at an early stage published papers on the metabolism of Vitamin D and sodium.

He might be regarded as one of the pioneer physicists and was a member of the Institute for many years serving on Council from 1950 to 1953.

A happy marriage came late in life, but was unfortunately cut short by a tragic road accident in which his wife was killed and he was seriously injured.

In his retirement he travelled widely and became interested in local activities, giving scientific advice to the R.S.P.C.A. and on educational projects.

R. HERBERT.

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THE BRITISH JOURNAL OF RADIOLOGY

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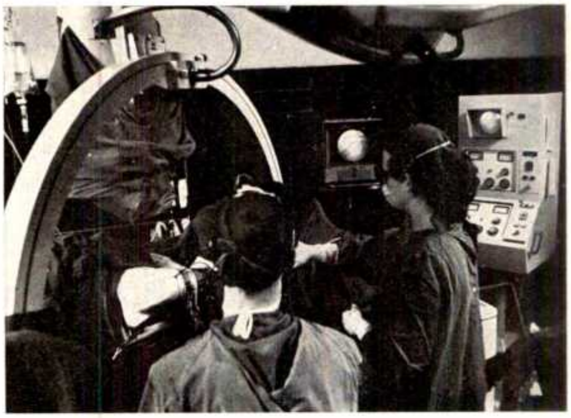

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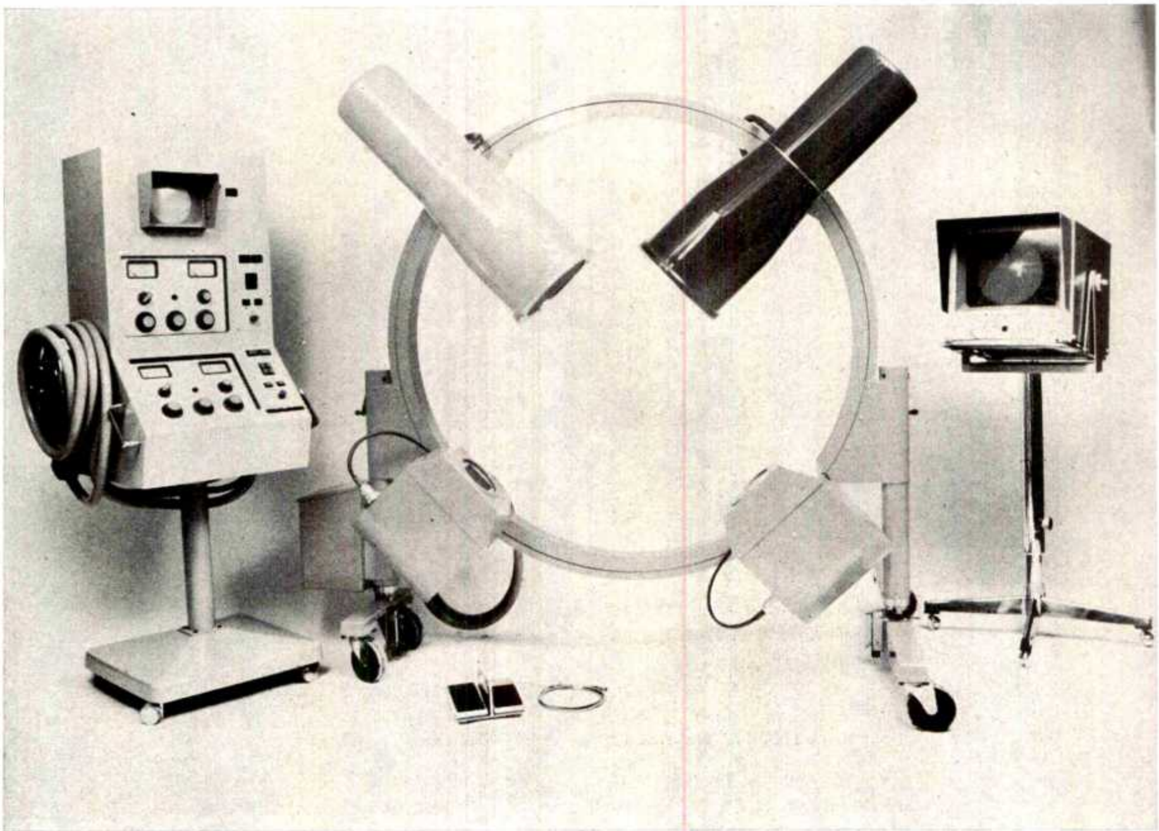

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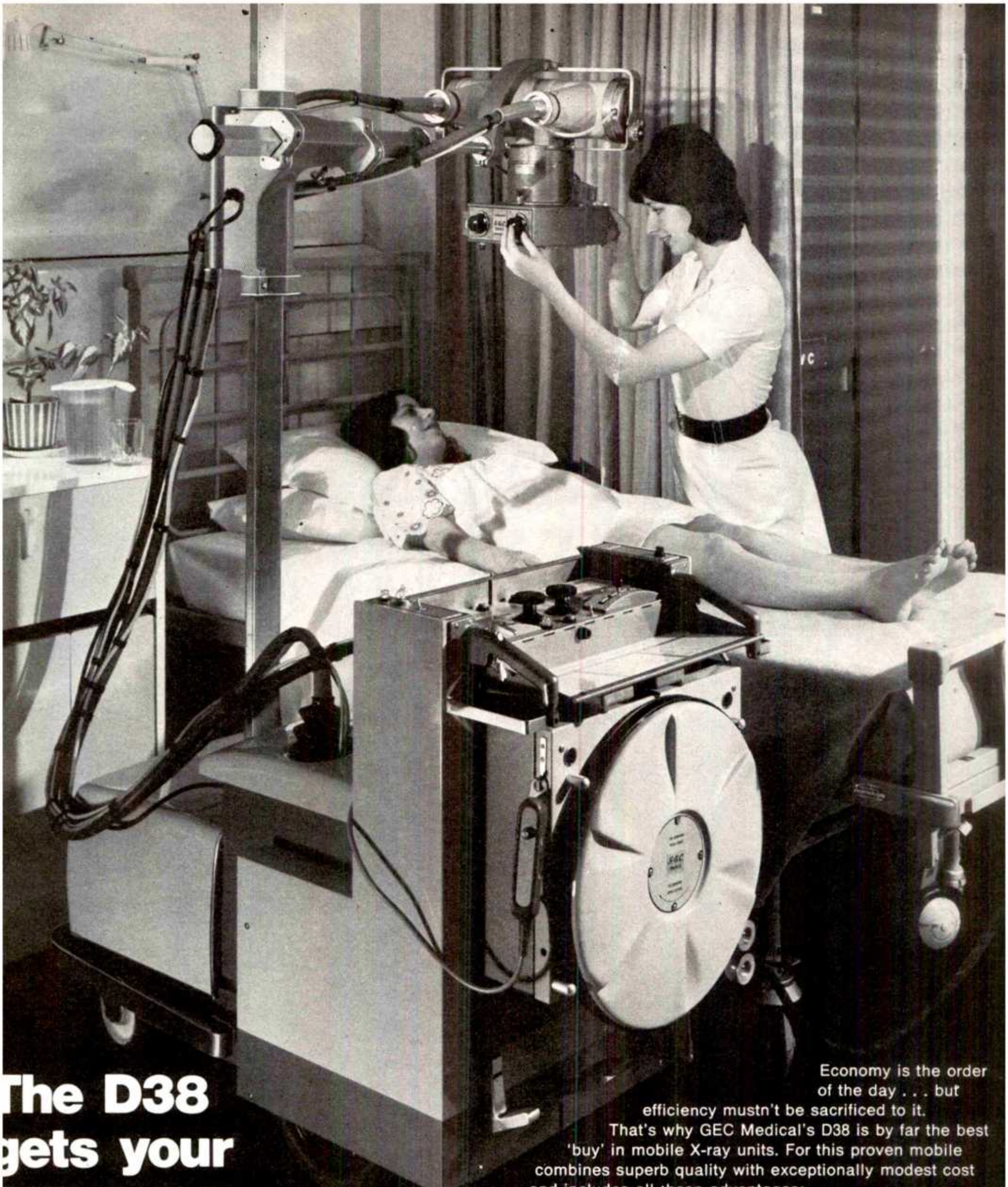

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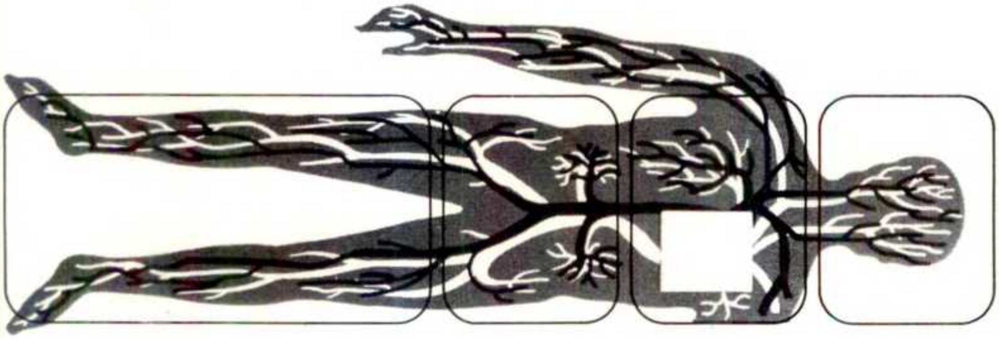

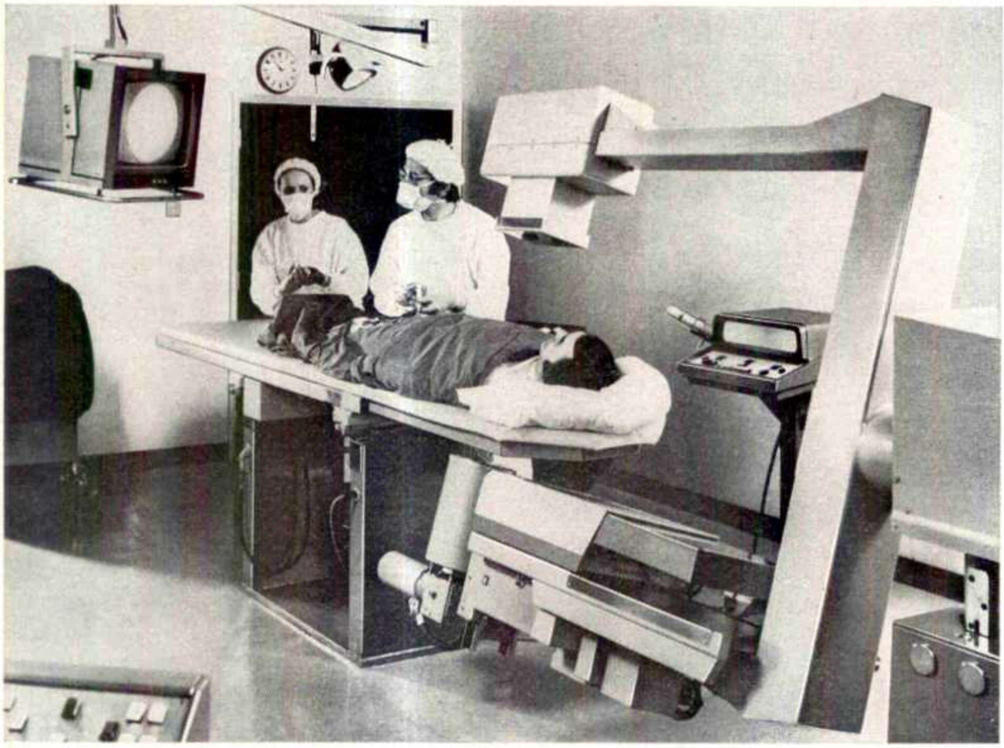

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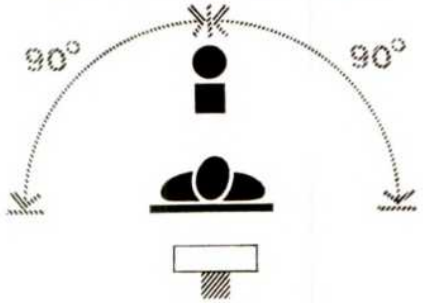

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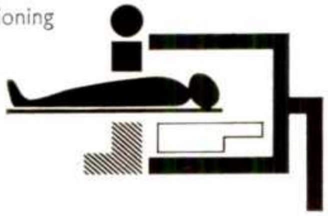

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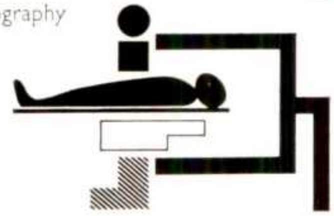

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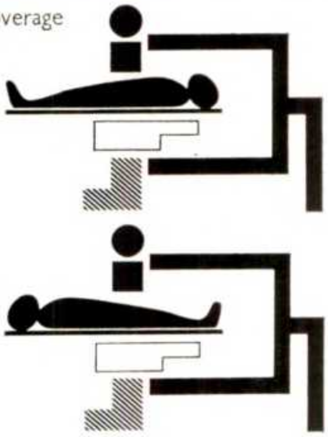

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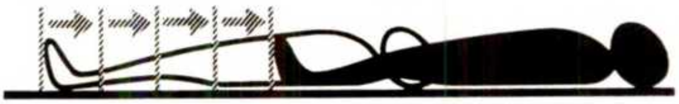

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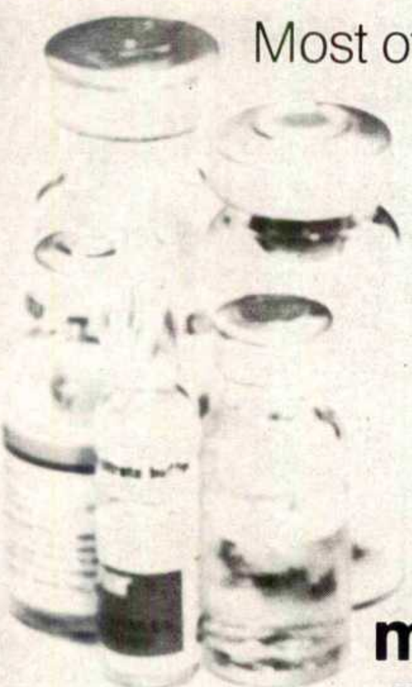

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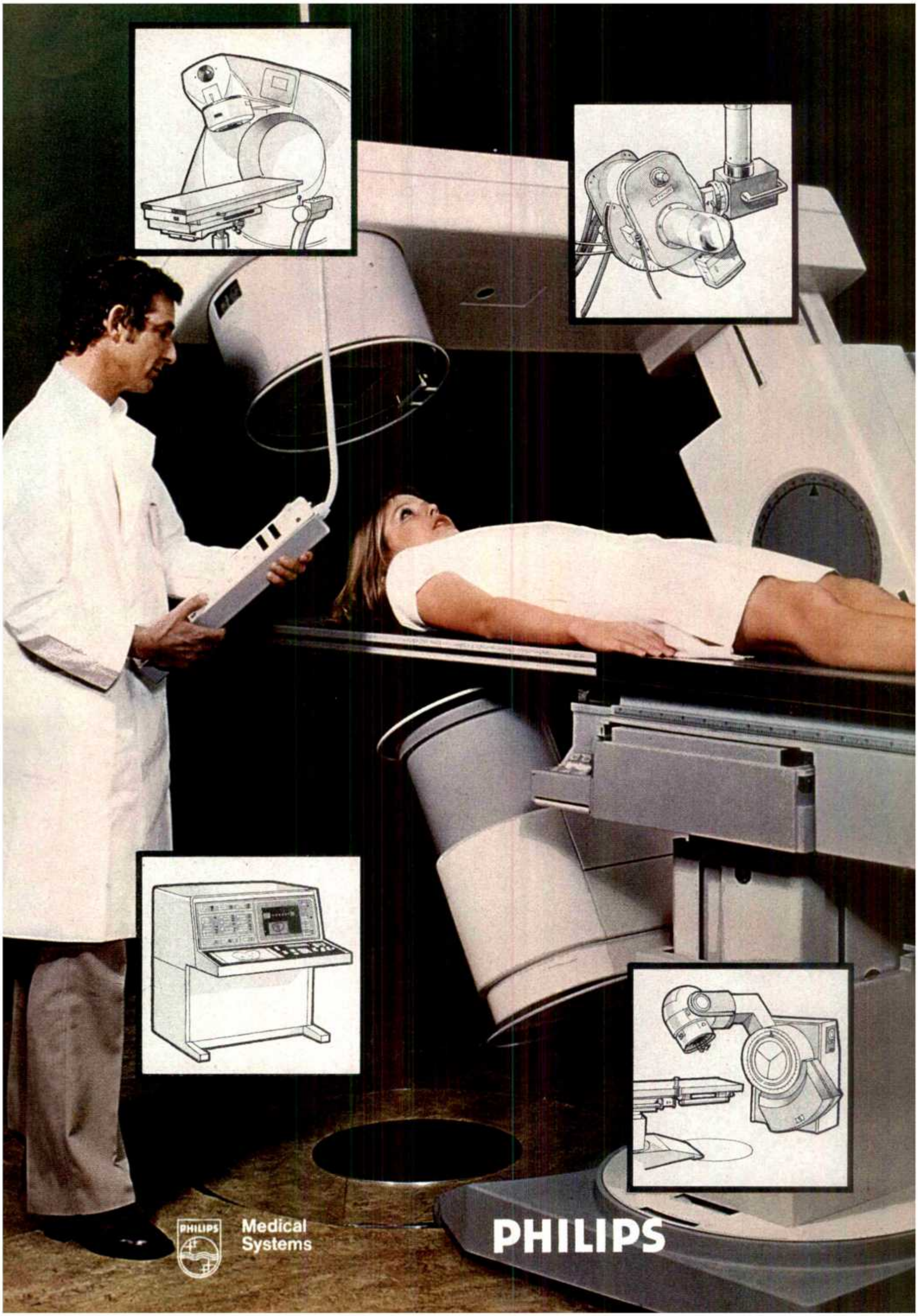
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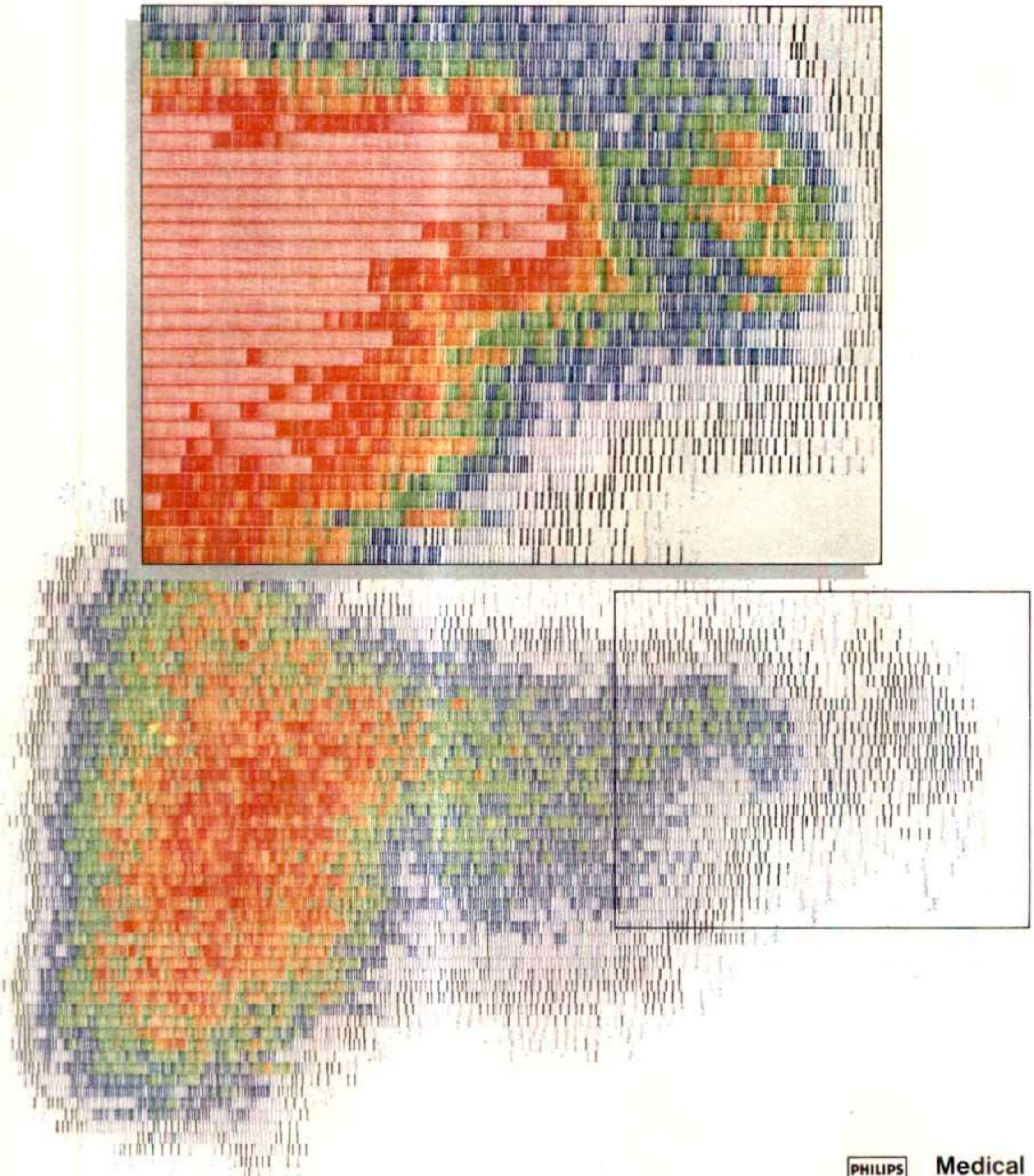

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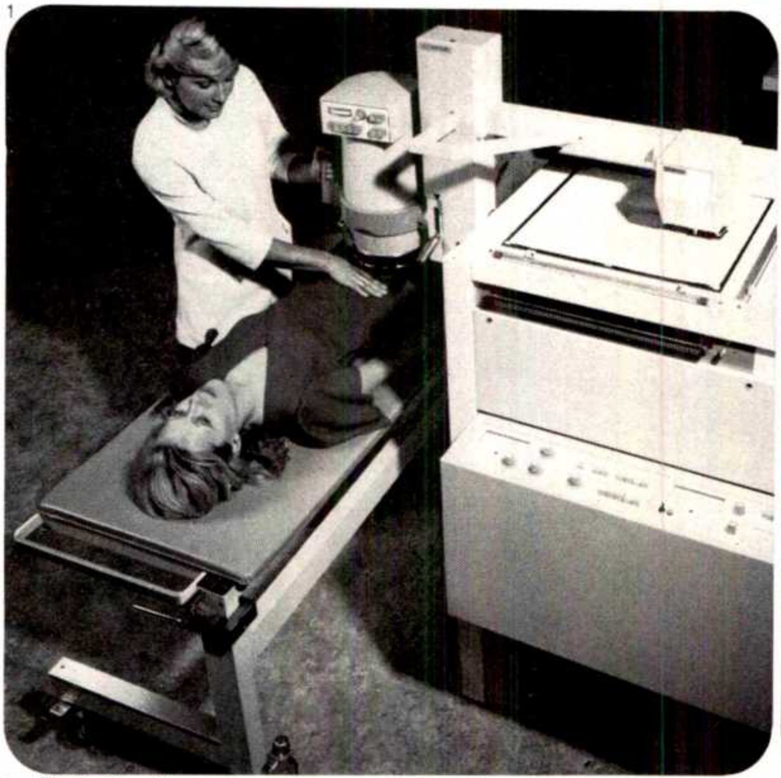

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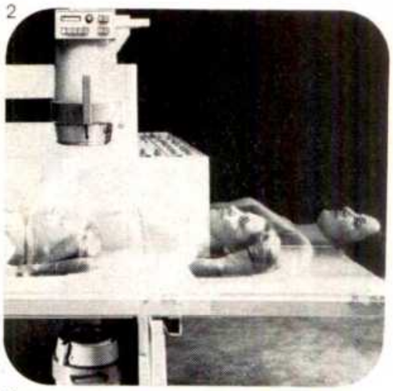

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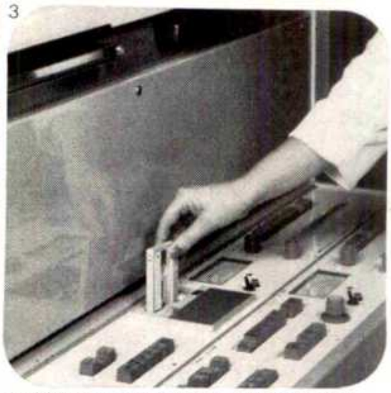

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2 **Total body and profile scanning** can also be performed by means of an optional motor-driven tabletop. This enables two-speed longitudinal movement of 100mm/min (approx. 4in./min) and 200mm/min (approx. 8in./min) and facilitates profile scanning using slit collimators. With the total body version the scanning area is 400 x 1600mm (15¾in. x 63in.); scintigram reduction factor being 4:1.

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3 **A second colour printer and photo scan unit** considerably extends the versatility of the Philips Universal Scintillation Scanner by enabling other original scans, based on different parameters, to be obtained. Furthermore, recording and storage of original scanning data can be achieved by means of a four track compact-cassette recorder. In the playback mode recordings can be reproduced using different scanner settings, i.e. different colour printer control signals.

Part of a complete programme of nuclear medicine equipment and systems, and fully supported by an international service organisation, the Philips Universal Scintillation Scanner represents the perfect integration of operational simplicity and efficiency with applicational flexibility and reliability.

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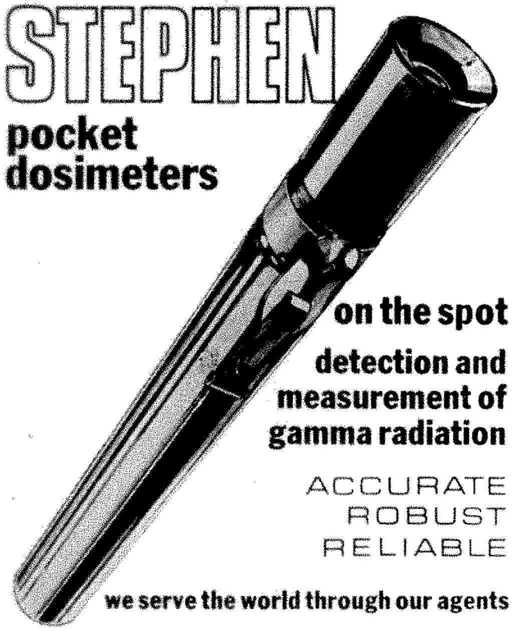

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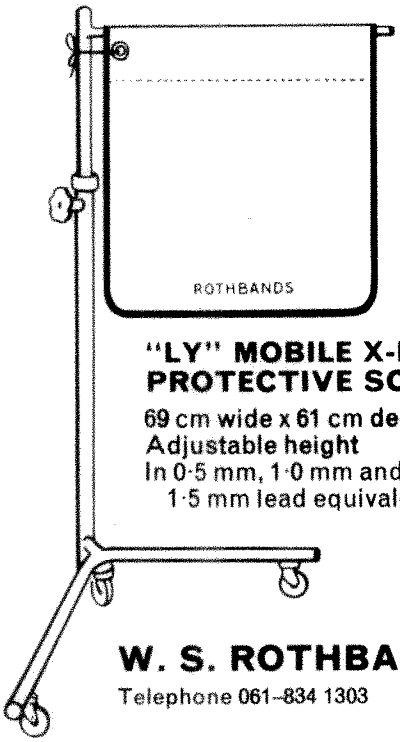

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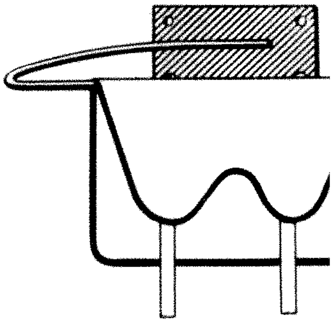

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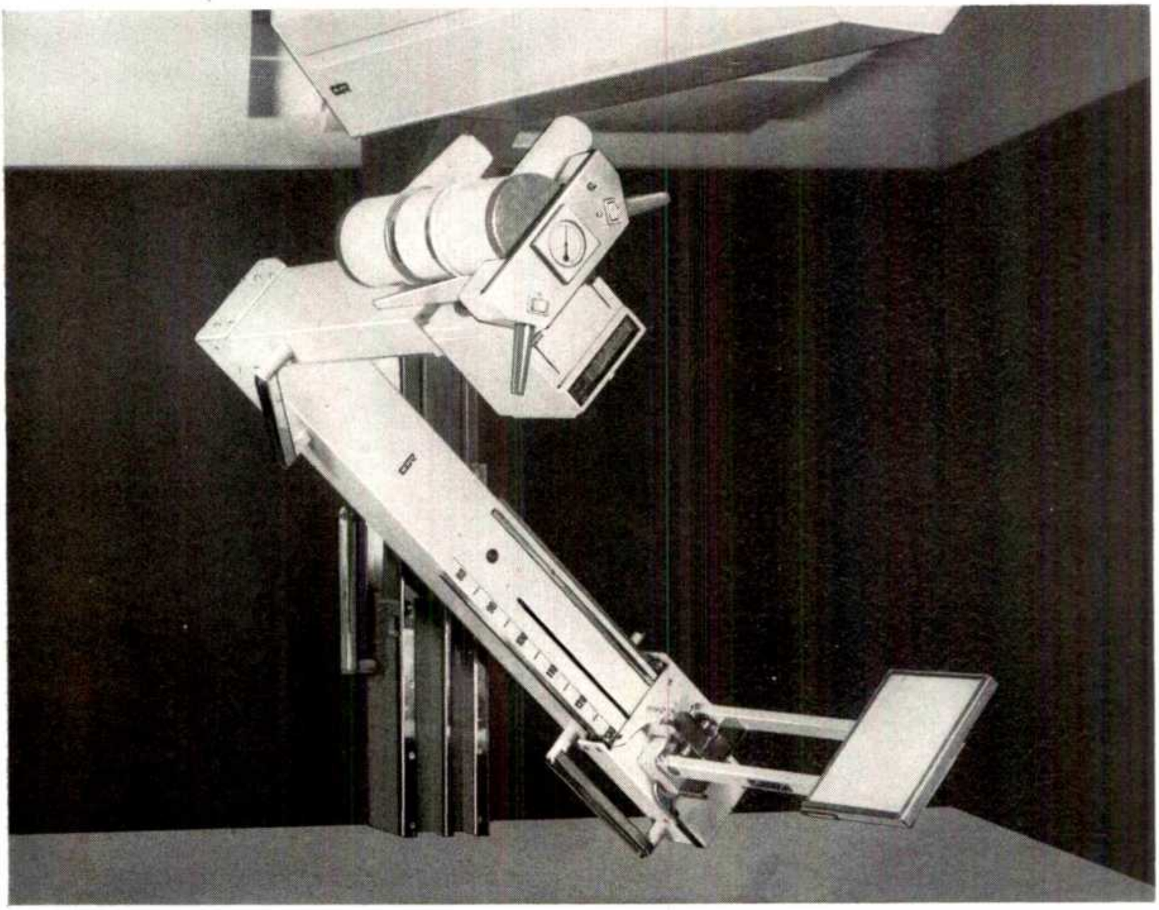

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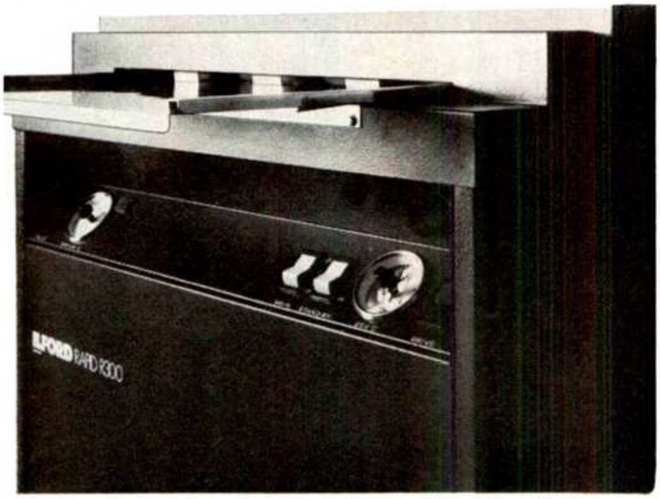

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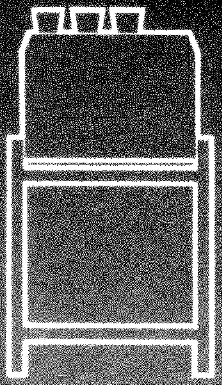

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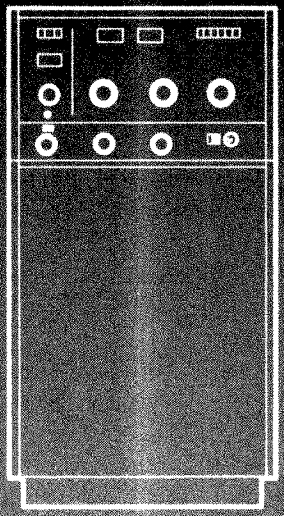

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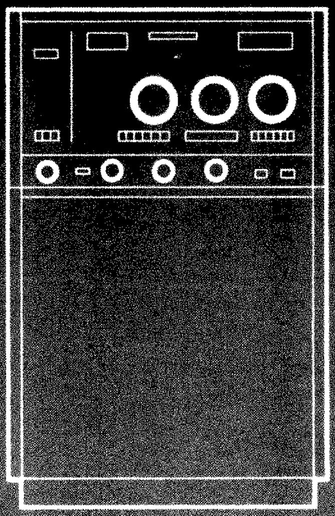

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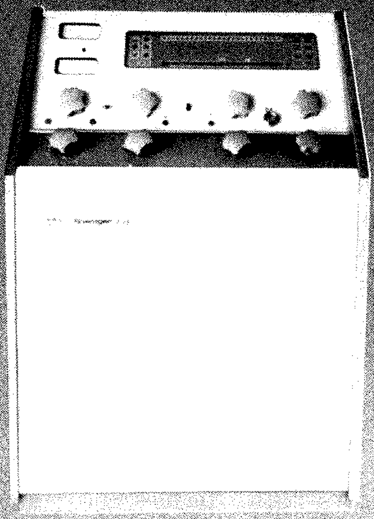

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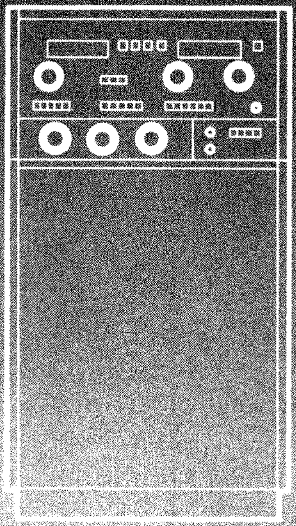

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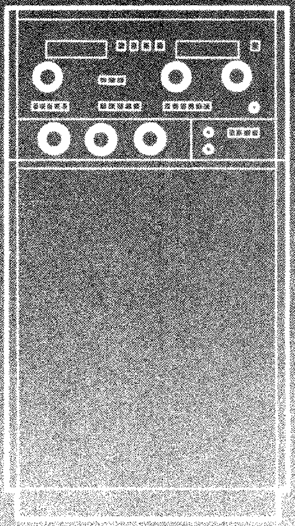

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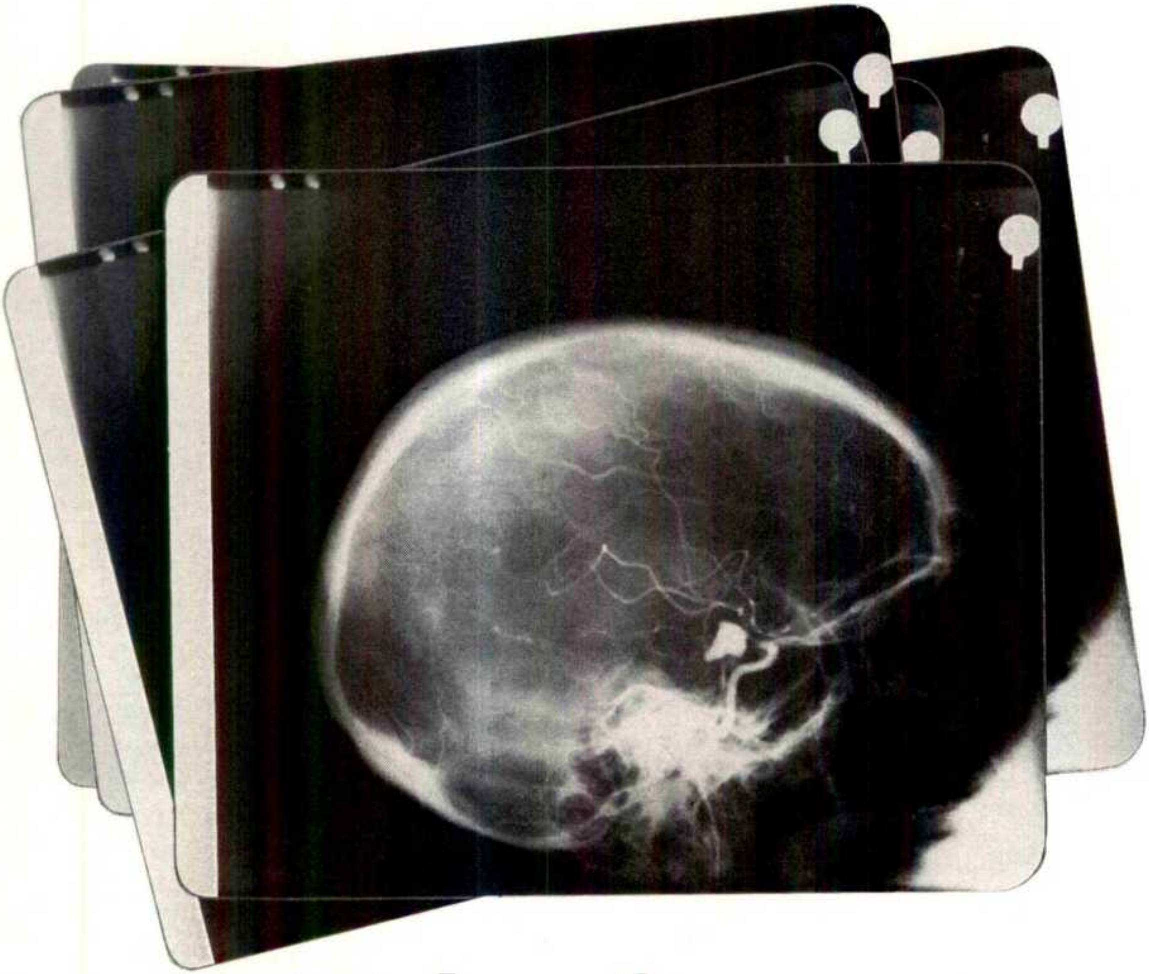

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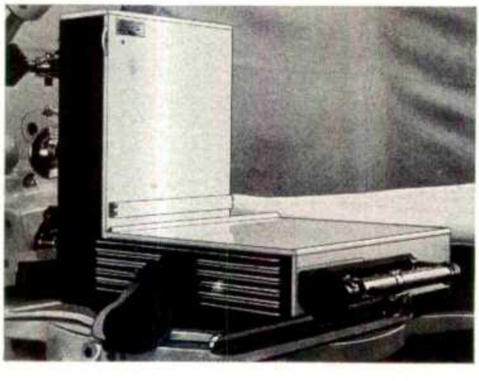
The Barr & Stroud Rapid Cassette Changer is designed to permit rapid serial angiography by *manual* operation – five exposures can be obtained at the rate of one a second.

The instrument can be easily mounted on either a Schonander or a Barazzetti skull table, and provides vibration-free x-ray photographs.



The 'L' method of construction compensates for beam divergence, and makes it unnecessary to raise the head on pads to ensure posterior coverage – or to reposition for taking AP views.

Full technical specifications and literature is available.

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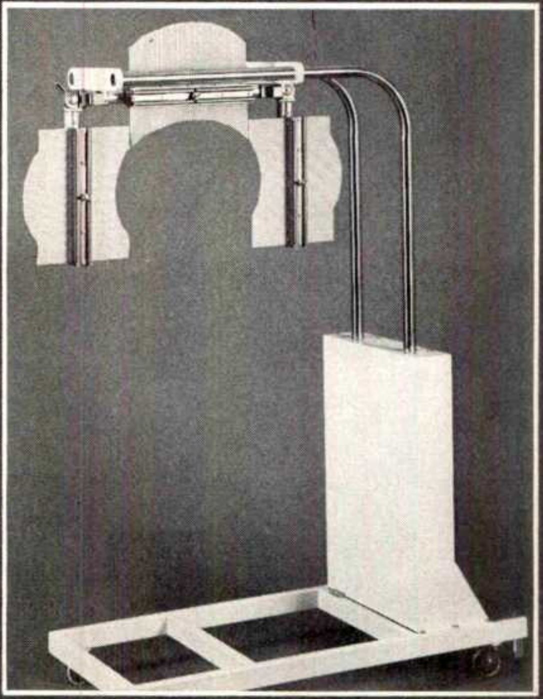
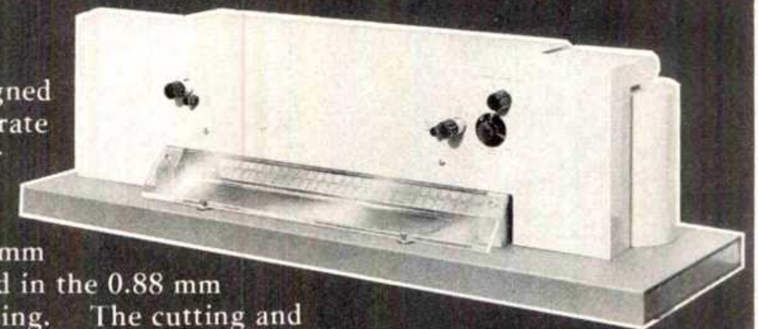
Formatron

The Formatron consists of 93 parallel anodised light alloy needles mounted between precision rollers. These rollers allow the needles to move freely and adjust accurately to the patient's profile. They are easily locked in position and when removed provide a perfect contour of the patient's outline.

A single Formatron may be used for small profiles. However, for a whole body contour, three Formatrons, mounted on a bracket assembly can be used. The three Formatrons can also be mounted on to an adjustable stand as illustrated and can be used in the Planning Room while the patient is in the supine position.



Iridium 192 wire encapsulator



The T.E.M. Instruments Limited Iridium 192 Wire Encapsulator has been designed to safely load and seal accurate lengths of 0.3 mm diameter Iridium 192 Wire into plastic tubing. Any length of wire from 5 mm to 300 mm can be cut and encapsulated in the 0.88 mm diameter technyl nylon tubing. The cutting and encapsulation is carried out behind 55 mm thick lead blocks which protect the operator throughout the entire loading procedure.

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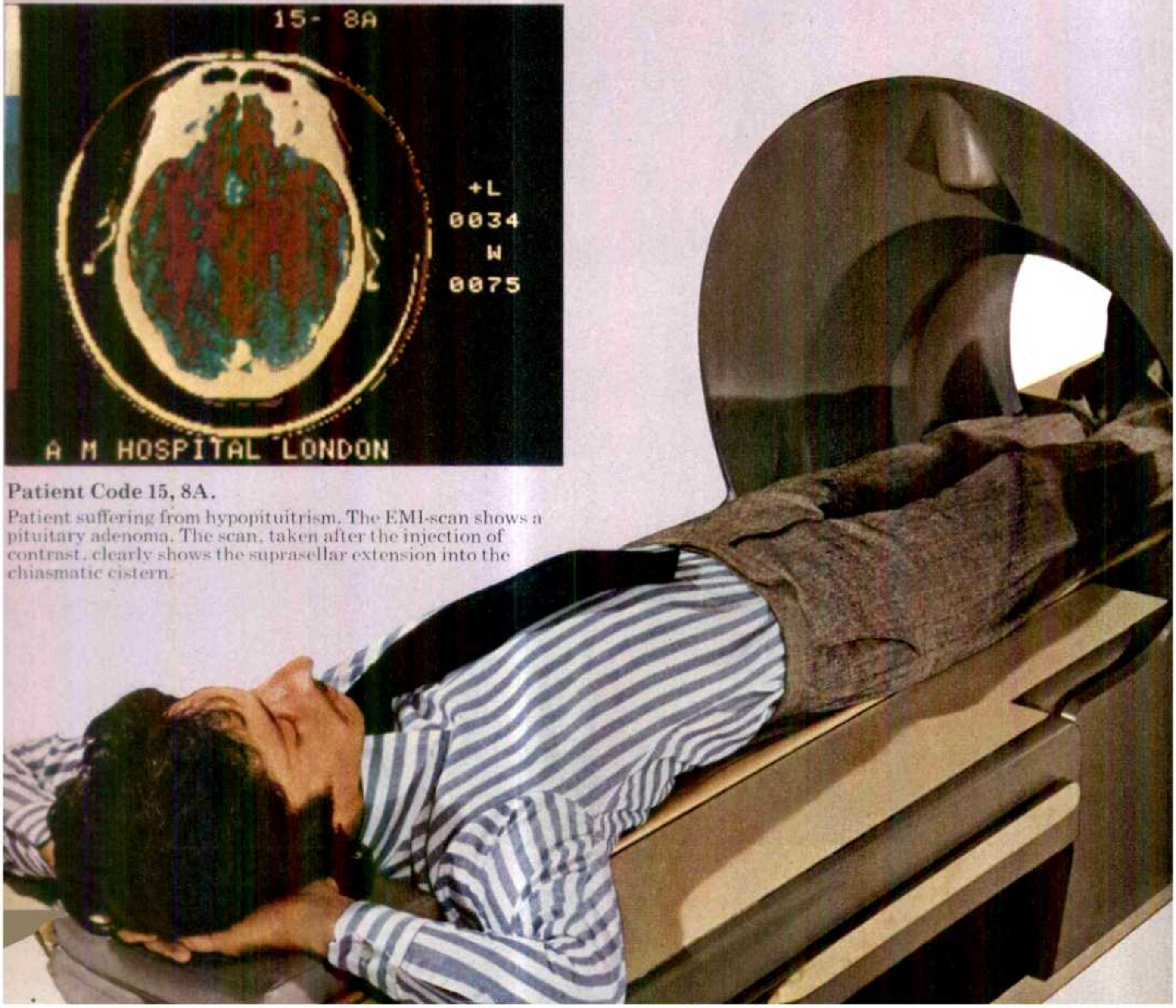
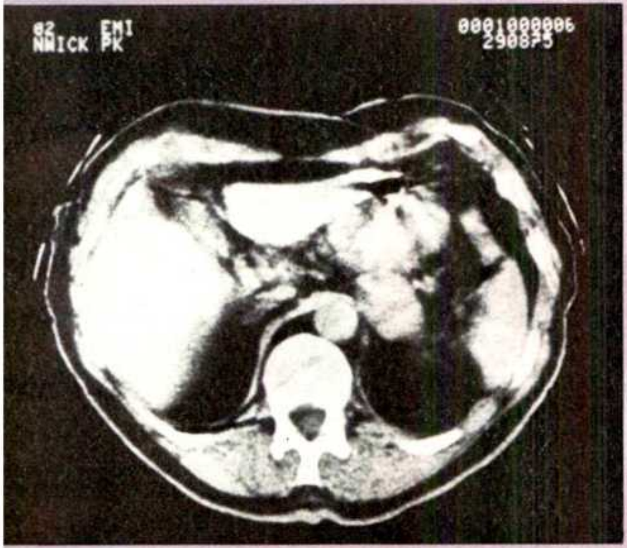
The case histories illustrated demonstrate the clinical capabilities of EMI-Scanner systems **in clinical use now,** fully evaluated, fully supported by our worldwide installation training and maintenance organisation.



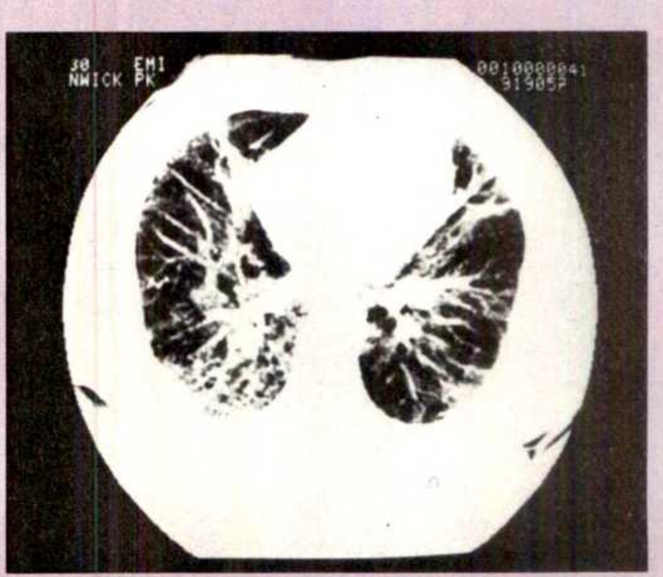
Patient Code 15, 8A.

Patient suffering from hypopituitrism. The EMI-scan shows a pituitary adenoma. The scan, taken after the injection of contrast, clearly shows the suprasellar extension into the chiasmatic cistern.

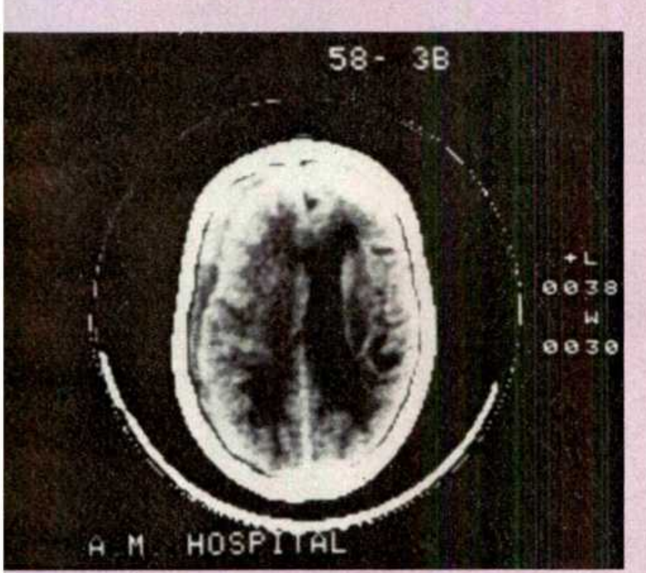
or selecting EMI~Scanne



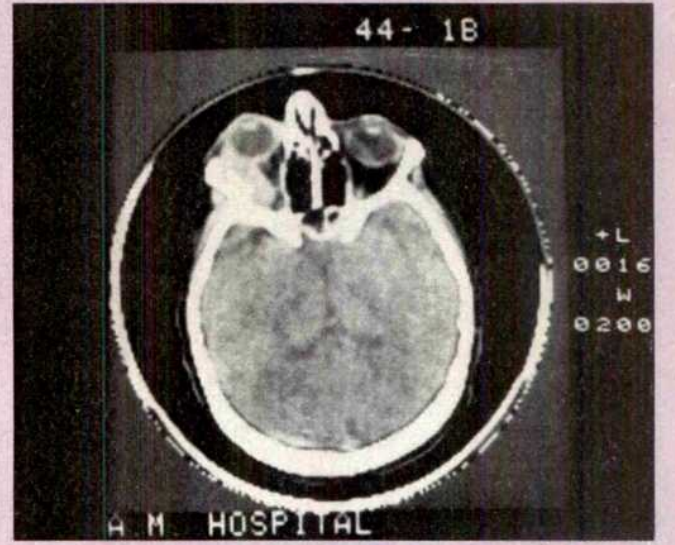
an 02.
n through 1st lumbar vertebra, demonstrates pancreatic
t.



Scan 30.
This scan clearly demonstrates interstitial fibrosis in the lungs. Due to the short scan time of the CT5005, the patient was able to suspend respiration for the duration of the scan, thus allowing the lung vessels to be clearly demonstrated without blurring.



tient Code 58, 3B.
year old female with a history of two falls in the month
vious to admission. She was admitted in a confused and
wsy state. The EMI-scan clearly demonstrates a left
dural haematoma.
te: Scan taken in "high sensitivity" mode. Note the clear
ineation between grey and white matter.



Patient Code 44, 1B.
Young male patient with a 12 month history of increasing proptosis and limitation of lateral occular movements. Lately he has suffered from conjunctival oedema. The EMI-scan demonstrates a mass in the lateral section of the left orbit, with early calcification visible within the mass. Note the detail visible in the orbital regions.

1976

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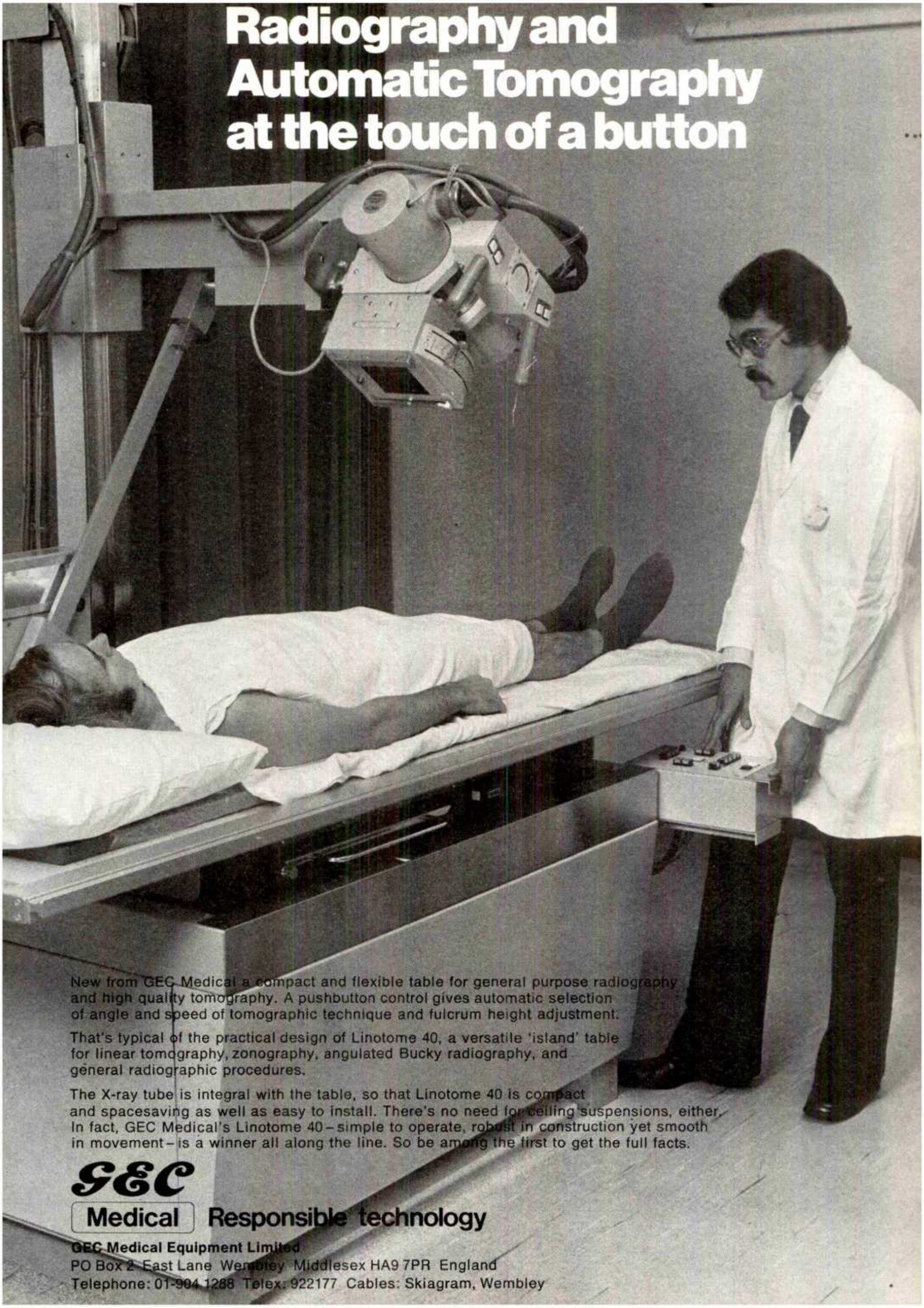
NE 4200 Diasonograph in operation in Princess Mary Hospital, Newcastle-upon-Tyne.



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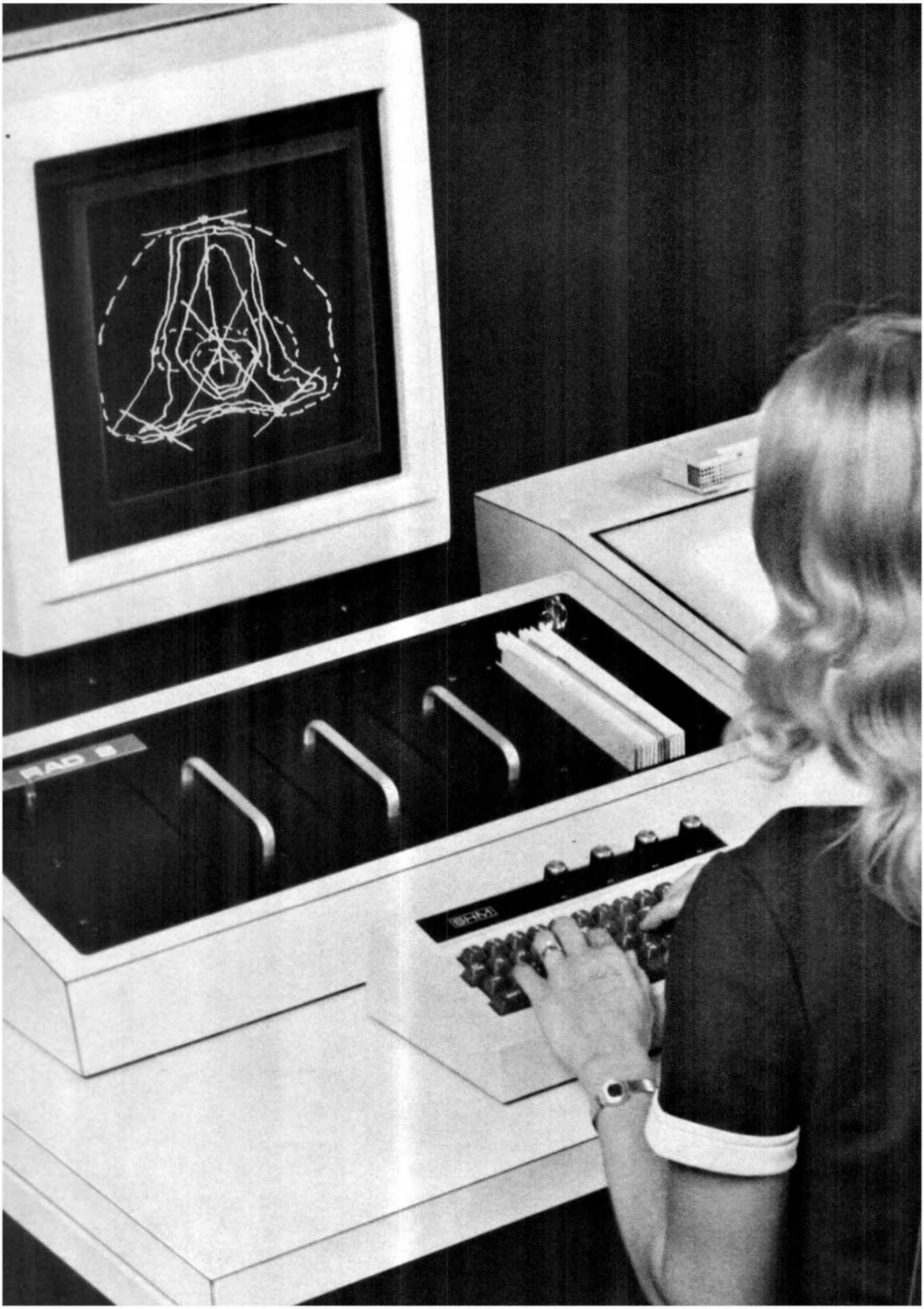
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The journal will be a vehicle for the rapid publication of original research papers, review articles, and preliminary publications in the field of computerized tomography. Papers published in the journal should be of interest to radiologists, neurologists, neurosurgeons, ophthalmologists, proctologists, nephrologists, oncologists, and specialists in internal medicine.

All articles submitted for publication to COMPUTERIZED TOMOGRAPHY will be reviewed for scientific merit and style of exposition. The journal will be quarterly at the outset, with the possibility of increasing to six issues per year should the volume of contributions warrant.

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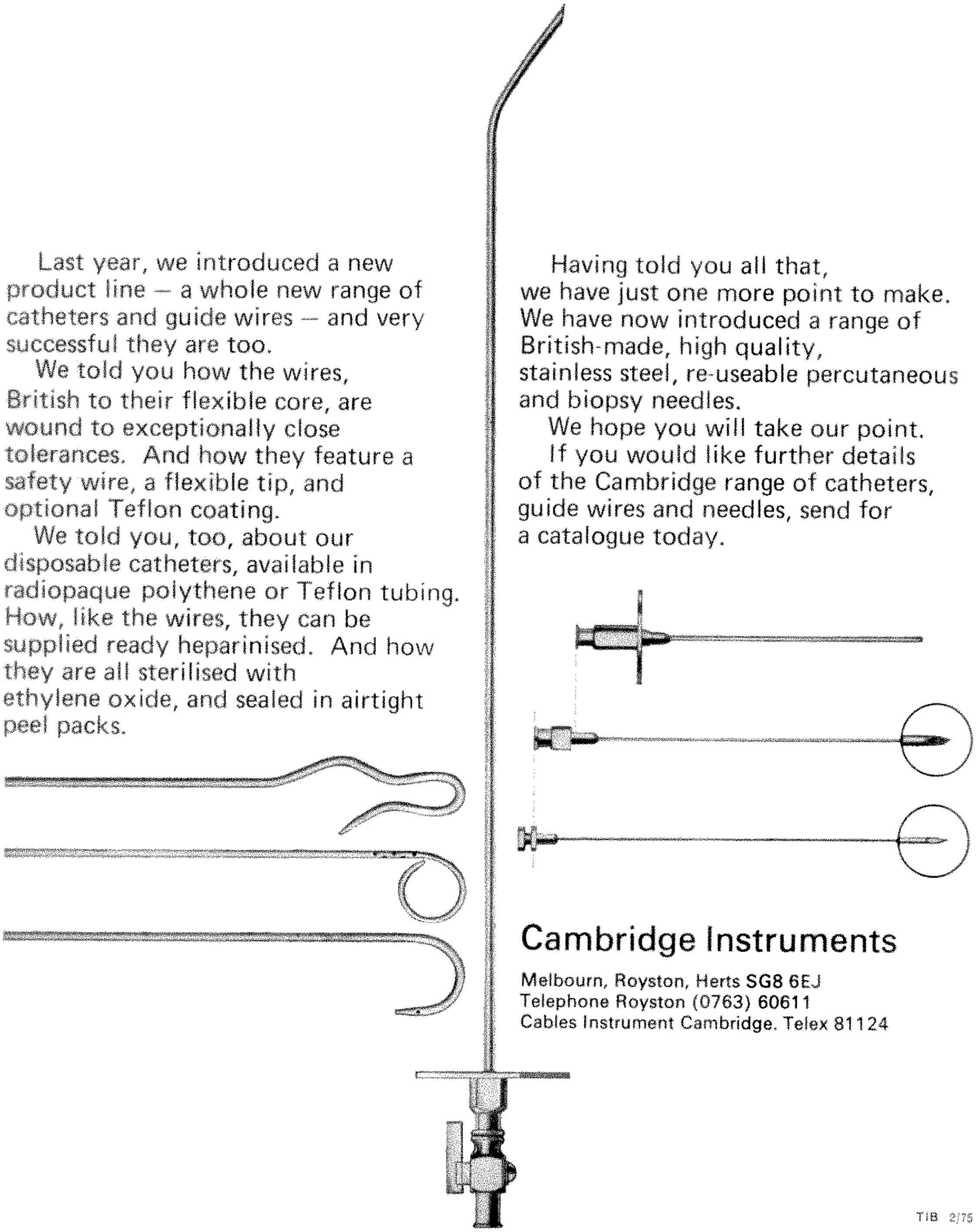

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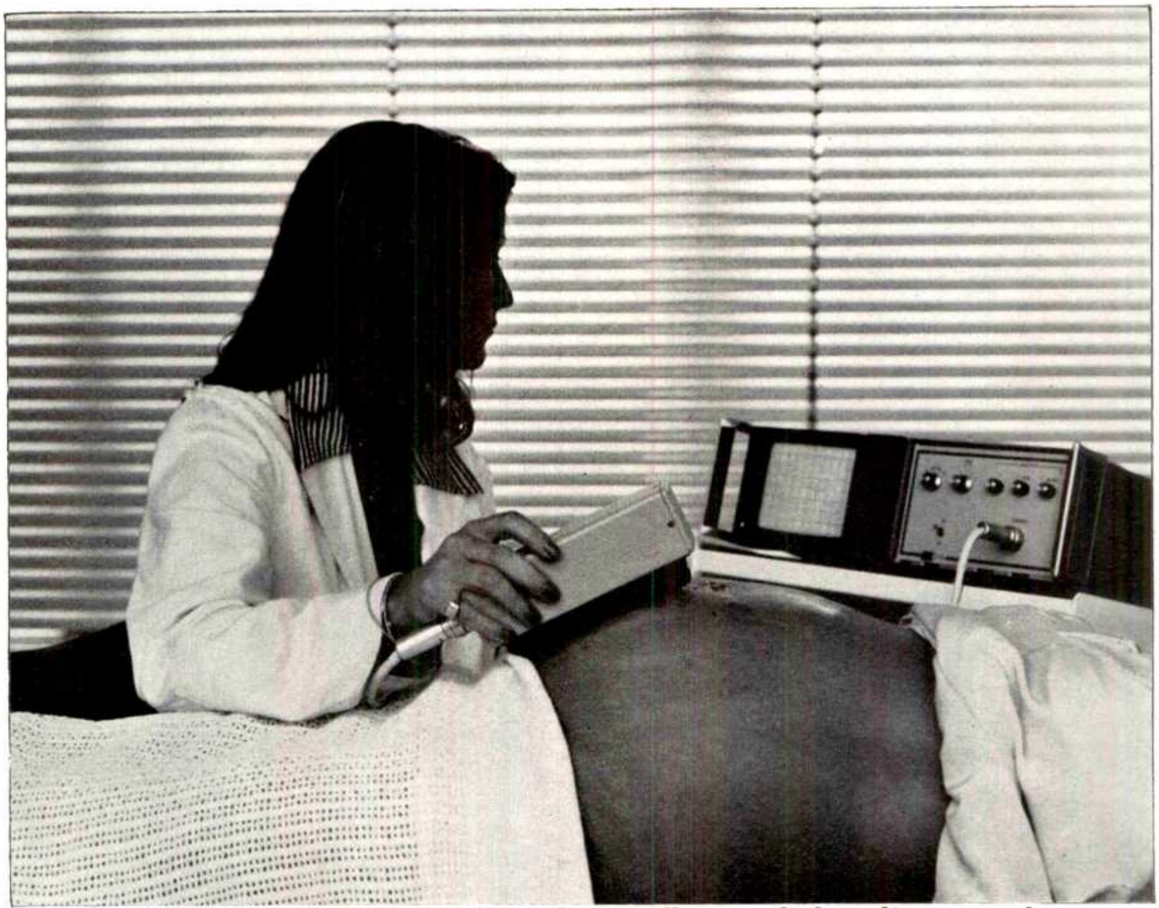

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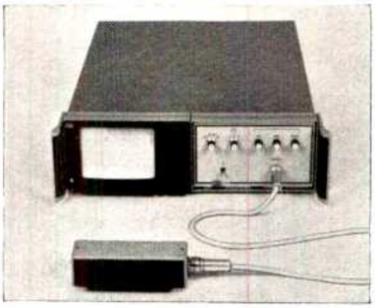

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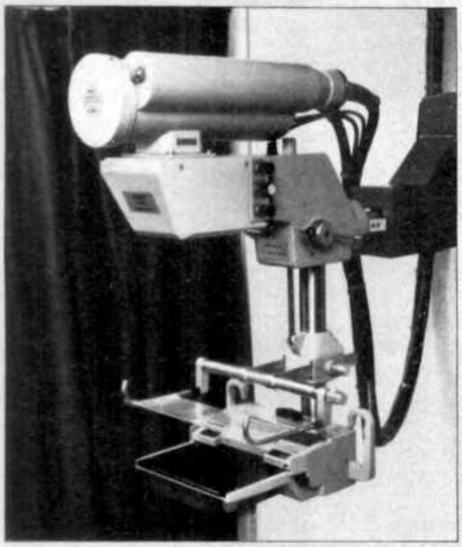

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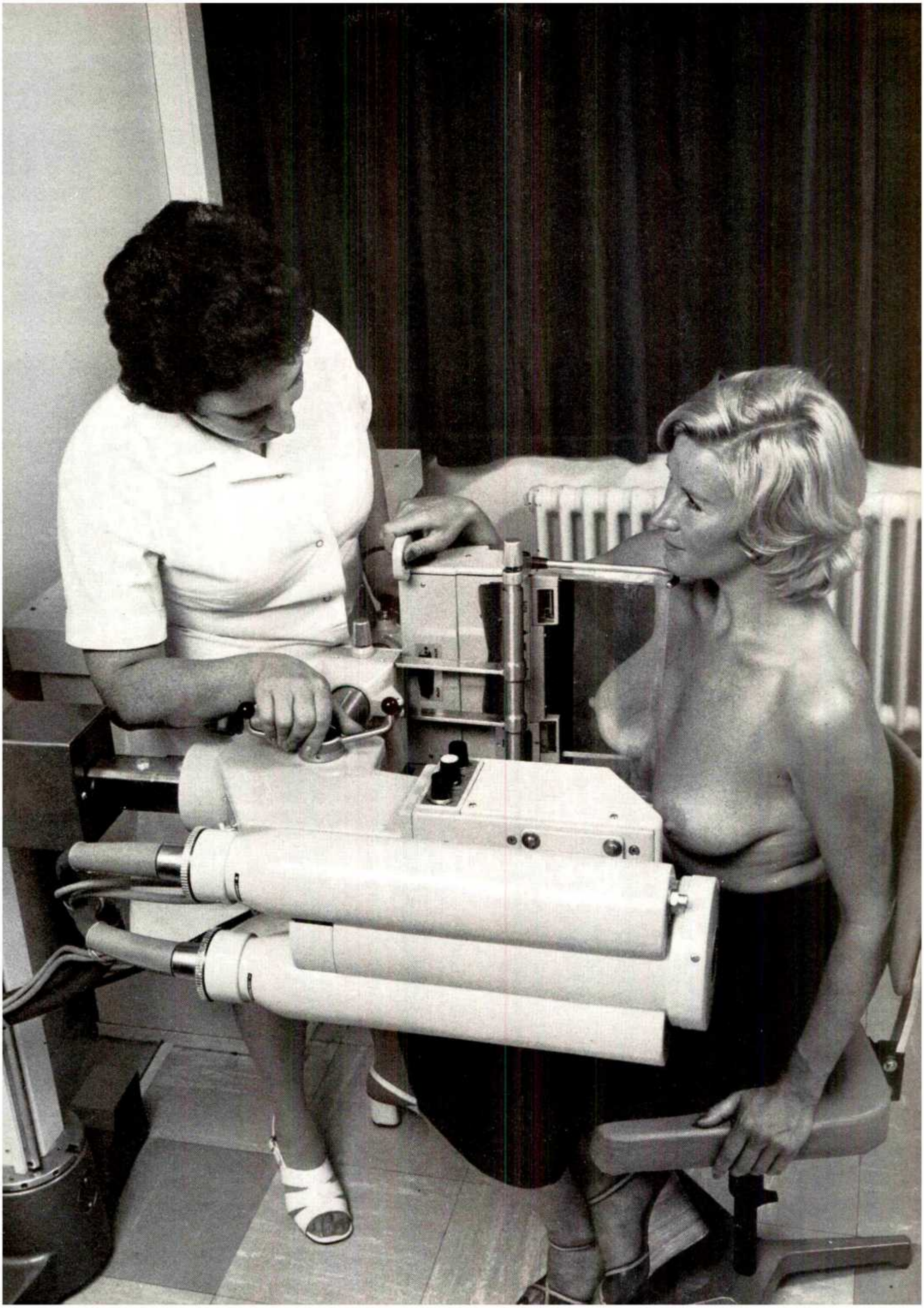

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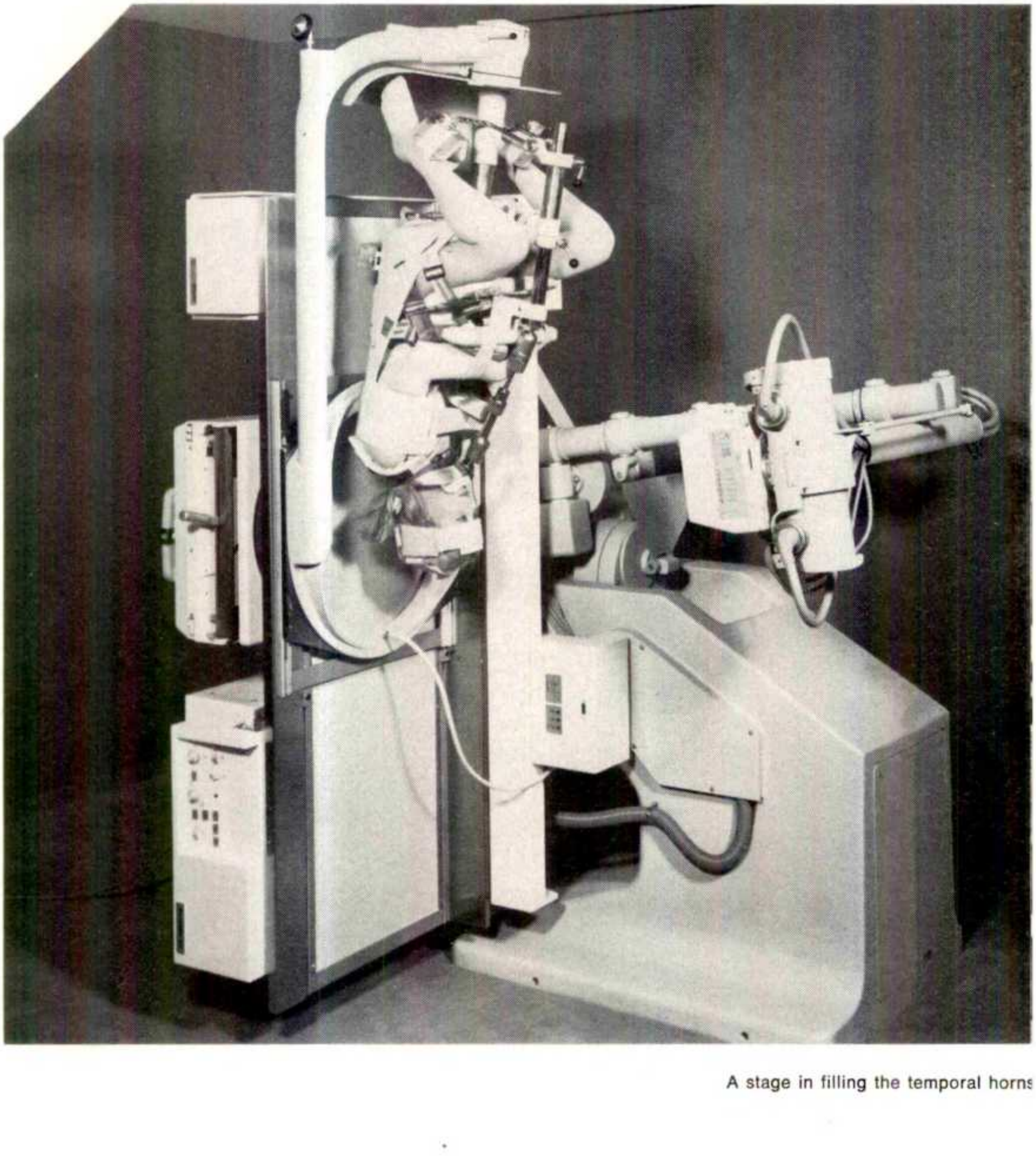

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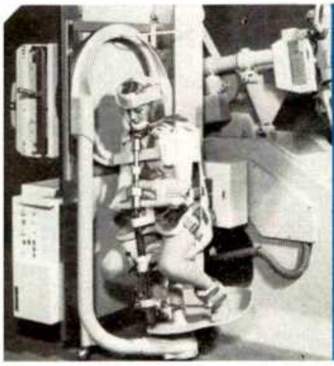

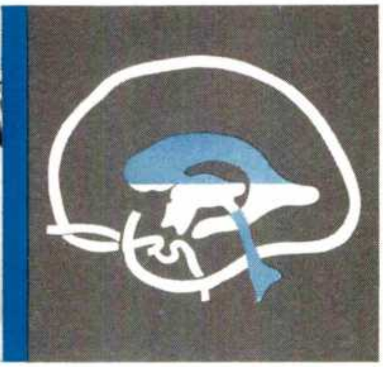

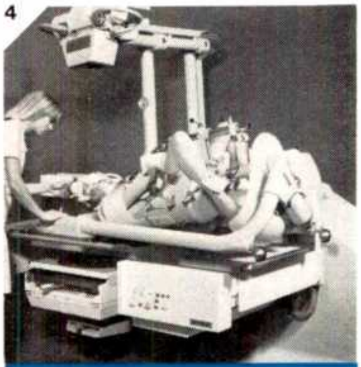

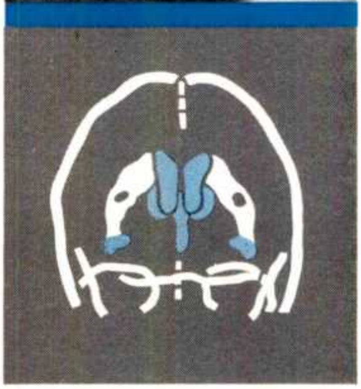

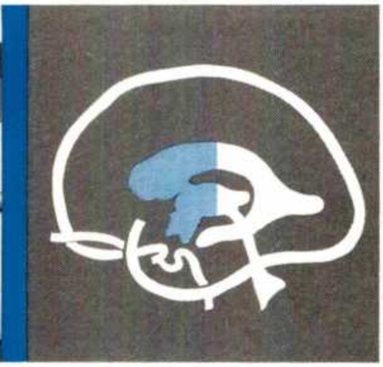

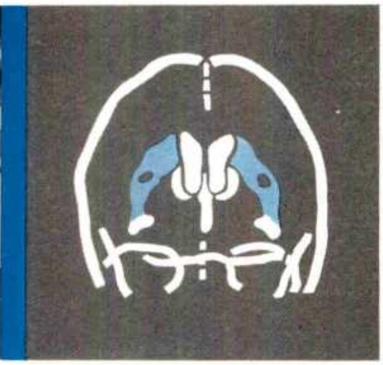

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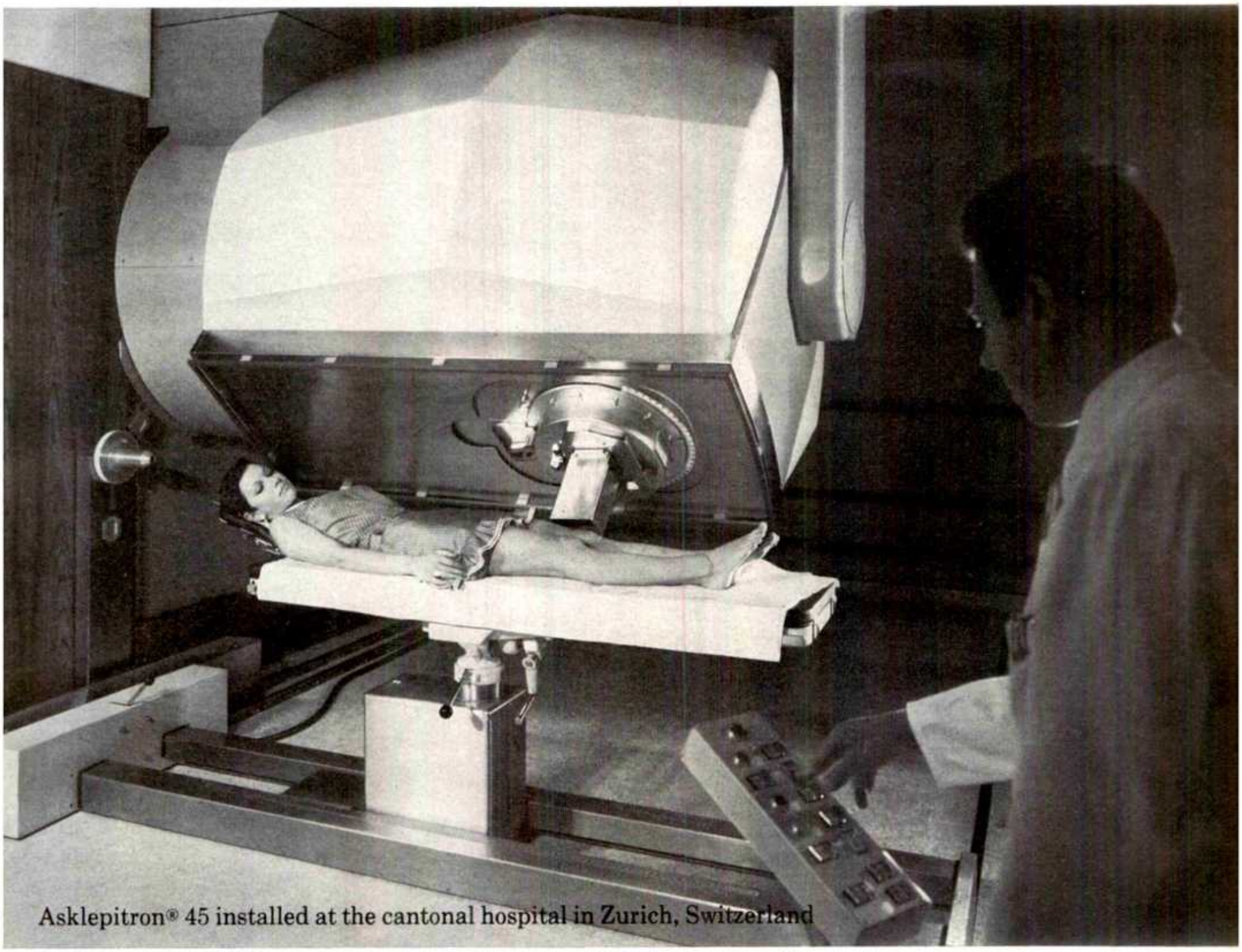

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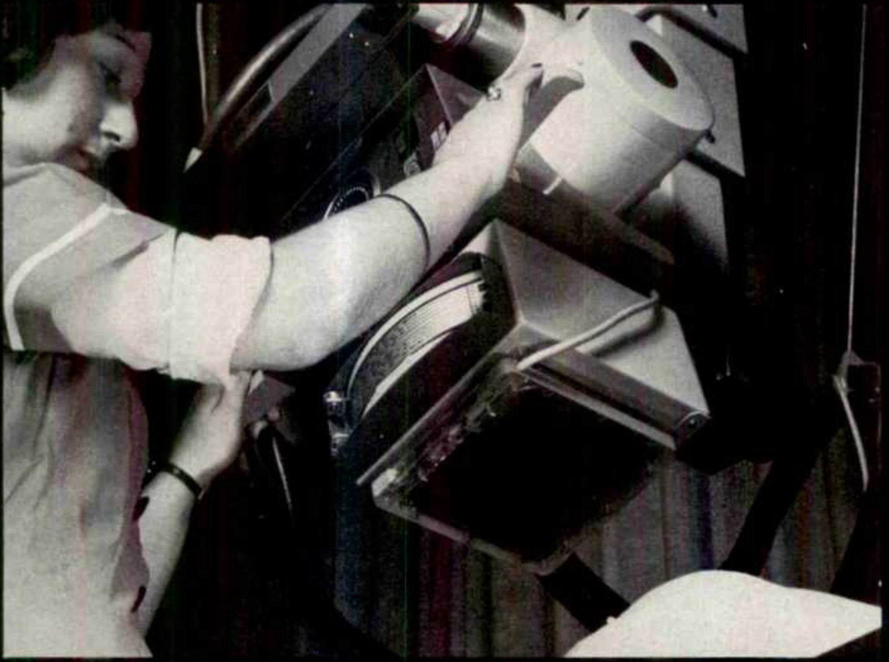

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The Pathogenesis of Reflux Nephropathy

By Professor C. J. Hodson, T. M. J. Maling, P. J. McManamon and M. G. Lewis

The association between vesico-ureteric reflux and renal damage has been recognized for some time, but it has usually been assumed that the damage is due to infection promoted by the reflux. However, observations by Rolleston and his colleagues in New Zealand have indicated a link between the severity of reflux and renal damage. Furthermore they have suggested that reflux penetrating into the renal substance is the factor most likely to explain the production of renal scarring.

These observations have been given a firm experimental basis by Professor Hodson and his associates. Their careful work on the growing pig has shown that the sites of intra-parenchymal or intra-renal reflux (I.R.R.) are the sites of subsequent and atrophy. I.R.R. only occurs above a critical pressure level; reflux at lower-pressures produces no evident damage. Infection aggravates scarring, but in the presence of I.R.R., scarring can occur with sterile urine.

The work set out in this monograph has wide practical implications, and is of interest to paediatricians, nephrologists, urologists, radiologists and others concerned in the management of patients with urinary tract infection.

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1976, *British Journal of Radiology*, 49, 901–902

VOLUME 49 NUMBER 587 NOVEMBER 1976

The British Journal of Radiology

Notebook

Review of current German radiological literature

W. A. Fuchs, M.D.

Department of Diagnostic Radiology, University Hospital, Bern, Switzerland

Preparing this third brief periodical survey of significant papers of the German radiological literature has provided a welcome incentive against indolence during the holiday season. It offered again the chance of making a selective review of advances in medical radiology during 1975 as recorded in the leading journals printed in German. The subjective character of such a selective review is obvious. While the selection includes some new data, much more of it represents confirmation and elaboration of previous achievements. An analysis of its content might well contribute to an understanding of the psychology of a regular reader of radiological journals, by indicating the contributions selected for comment when a mainly diagnostically orientated radiologist is given a free hand in making his own selection of medical radiology papers published in his native literary language.

The value and use of percutaneous transthoracic needle biopsy of intrathoracic disease are carefully evaluated, based upon 5300 studies (Sinner, 1975). Needle biopsy proved to be technically simple and relatively safe; it permits early diagnosis of bronchial carcinoma and solitary metastases with a high degree of accuracy, and with few complications. The author assumes that, as a result, the prognosis of patients with bronchial carcinoma in the pre-clinical stage may be markedly improved. Needle biopsy under fluoroscopic or ultrasonic guidance of various organs such as the lung, kidney, pancreas, liver, lymph-nodes and breast is one of the major advances of diagnostic radiology in recent years—a directly aggressive approach to get information about the histopathological structure of lesions, which may usually be detected by non-invasive radiological methods. This policy of getting right to the heart of the matter is certainly economical and eliminates expensive diagnostic speculations.

Computerized transversed axial tomography has eventually come into use in Germany, Austria and Switzerland. A few of the first results have been published (Hacker and Becker, 1975), and symposia on this subject are scheduled. The Siemens firm has developed its own apparatus for CAT of the brain (Führer *et al.*, 1975) a possible challenge to the EMI-scanner.

Data on a new compound for cholangiography (Iotroxamide) (Taenzer *et al.*, 1975) indicate that the maximal transport capacity of the liver for this substance is higher than for the currently used products, and that the visualization of the biliary tract is, therefore, significantly improved. Careful clinical studies of the pharmacokinetic action, in particular measurements of the maximal transport capacity of Iotroxamide, in addition to a well planned clinical trial of the diagnostic performance and patient tolerance are, however, still lacking.

A paper on epinephrine renal venography (Rösch *et al.*, 1975), published in English, and based on experience in 60 patients, suggests that this technique is of particular value in the diagnosis of avascular infiltrative tumours of the renal parenchyma and pelvis. According to the author, smoothly contoured, though deformed, veins may help in the differentiation of an expansive inflammatory mass from an infiltrative tumour. Large capsular and pericapsular veins are often seen around chronic inflammatory masses. Anyone dealing with such a difficult diagnostic case might well hope that these diagnostic criteria will hold for most of the questionable cases.

A detailed description of the angiographic findings in focal nodular hyperplasia of the liver may be of practical interest (Zurbriggen and Tylén, 1975). Although this condition is rare, knowledge of its angiographic appearance is important when hypervascular lesions within the liver parenchyma have to be evaluated. Focal nodular hyperplasia presents as a hypervascular benign expansive lesion, with a typical vascular structure and intensive, prolonged and sharply demarcated parenchymal staining.

The changing pattern of lesions in colonic

Crohn's disease, studied in 86 patients, is presented in "Dynamic aspects of colonic Crohn's disease" (Brahme and Fork, 1975), another paper published in English. Local progression was observed as an unpredictable event in most cases; temporary regression was rare. Post-operative spread or recurrence and spread was present in 25% in this series. Since inflammatory disease within the submucosa causing minute ulcers is considered to be a cause for the high post-operative recurrence rate, angiographic demonstration of hypervascular inflammatory changes may well give more detailed information about the extent of the disease and thus help to decrease the recurrence rate (Voegli *et al.*, 1976).

Several views on subjects such as renal hypertension (*Radiologe*, *15*, 4, 1975), pancreas (*Radiologe*, *15*, 5, 1975), colon (*Radiologe*, *15*, 11, 1975) and treatment planning in radiation therapy (*Radiologe*, *15*, 6, 1975) are well worth reading, and not only because some of the papers are written in English.

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Journal review

Journal de Radiologie

This new journal is the official publication of the French Neuroradiological Society. The papers are based on the proceedings of the meetings of the Society with emphasis placed on illustrations, especially radiographs accompanied by detailed legends, the text being kept relatively brief. The journal appears quarterly and is published in both French and English in adjacent columns.

The first volume presents a review of systematized angiodysplasias. Not only are the abnormalities in the head, neck and spinal cord described in detail, but there is also discussion of the changes in the systemic and visceral vessels. All the material is carefully selected and there is much pathological correlation.

Now that there are so many journals containing neuroradiology, it may be questioned whether a further one should have been launched. However, the excellent work that has been performed by French neuroradiologists during recent years and the high standard of the first volume should dispel any fears on that score. The journal is strongly recommended to any radiologist with a special interest in the neuro sciences.

B. E. Kendall.

1976, *British Journal of Radiology*, *49*, 903–911 NOVEMBER 1976

The clinical significance of pneumographic cerebellar atrophy

By P. Kennedy, M.B., M.R.C.P., M. Swash, M.D., M.R.C.P., and I. G. Wylie, F.R.C.S.(E), F.R.C.R.

Departments of Neurology and Radiology, Section of Neurological Sciences, The London Hospital, London E1 1BB.

(*Received June, 1976*)

ABSTRACT

The clinical significance of apparent pneumographic cerebellar atrophy has been studied in a group of 44 otherwise unselected patients found to have cerebellar atrophy, according to previously suggested criteria, at pneumoencephalography. Lateral and postero-anterior tomography of the posterior fossa was performed in all these cases. In each case the width of two or more sulci in the cerebellar vermis exceeded 2 mm. We have concluded that:

(1) There is a relationship between the severity of pneumographic cerebellar atrophy and the severity of clinical signs of cerebellar disease ($p = 0.03$).

(2) Severe or moderate atrophy of the vermis, whether generalized or focal, is usually associated with clinical signs of cerebellar disease, but mild atrophy of the vermis, equivalent to the "moderate" atrophy of previous studies, has no apparent diagnostic significance.

(3) Atrophy of the cerebellar hemispheres, in the absence of atrophy of the vermis, is very unusual and it cannot, by itself, be correlated with clinical signs of cerebellar disease.

(4) In individual cases, assessment of the significance of pneumographic cerebellar atrophy cannot be made without adequate clinical information.

Cerebellar atrophy is sometimes found during pneumoencephalography in patients in whom there is no clinical suspicion of cerebellar disease. This, and the wider problem of the relation between pneumographic cerebellar atrophy and clinically apparent cerebellar disease, was studied by LeMay and Abramowicz (1965; 1966). Their radiological technique included sagittal autotomography and this enabled them to measure the width of sulci in the cerebellar vermis. They suggested that these measurements could be used as an index of cerebellar atrophy and, in particular, that cerebellar sulci greater than 2 mm in width indicated a "mild to moderate" degree of cerebellar atrophy, and that sulci greater than 4 mm in width were found only in the presence of "marked" cerebellar atrophy. These criteria were accepted by Robertson (1967). However, LeMay and Abramowicz (1966), using their criterion of sulcal width, found that there was no clinical evidence of cerebellar disease in 11 of their 28 patients with "mild to moderate" pneumographic cerebellar atrophy, and in one of their 11 patients with "marked" cerebellar atrophy. Despite this LeMay and Abramowicz (1965; 1966) criteria have been used in a number of subsequent reports of cerebellar atrophy (Momose *et al.*, 1971; Selhorst *et al.*, 1972; Strecker *et al.*, 1972). Sutton (1950), Amundsen and Grimsrud (1966) and Robertson (1967) have suggested that measurement of the height of the fourth ventricle might be useful but it has been found that the size of the fourth ventricle varies independently of the width of sulci in the cerebellar vermis (LeMay and Abramowicz, 1966; Selhorst *et al.*, 1972; Strecker *et al.*, 1972). Other measurements, particularly of the size of subarachnoid cisterns in the posterior fossa (Lilliequist, 1959), have proved unreliable indices of cerebellar atrophy, since the range of normal variation is wide (LeMay and Abramowicz, 1966) although Bentson and Alberti (1972) have commented that the subarachnoid cisterns are usually enlarged in cases of olivo-ponto-cerebellar atrophy.

In recent years we have used tomography in the lateral and postero-anterior planes as a routine procedure in pneumoencaphalography (Morris and Wylie, 1973), and have found apparently advanced cerebellar atrophy so frequently that we have been led to question the significance of the criteria put forward by LeMay and Abramowicz (1965; 1966) and Robertson (1967). In an attempt to resolve this problem in a retrospective study, we have compared the radiological and clinical features of a group of patients in whom apparent cerebellar atrophy has been found during pneumoencephalography.

MATERIAL AND METHODS

The pneumoencephalograms of 46 patients were studied. In all these patients there was cerebellar atrophy which was judged to be of *at least* "mild" to "moderate" severity, according to the criteria of LeMay and Abramowicz (1966). In all these patients, therefore, the width of two or more cerebellar sulci exceeded 2 mm. Patients with radiologically demonstrated posterior fossa tumours were excluded from the study. Two patients were not included in the series because their clinical notes were inadequate, and the patients themselves could not be traced. The remaining 44 patients consisted of 29 men and 15 women whose ages ranged from 31 to 82 years (mean 60 years). In attempting to correlate the radiological and clinical features of these patients assessment was made according to a series of standard criteria.

Radiological assessment. All the pneumoencephalograms had been carried out by one of two neuroradiologists (Drs. L. Morris and I. G. Wylie) using a Philips Diagnost-N apparatus, equipped with an isocentric chair. The procedure itself was standardized according to the technique previously described by Morris and Wylie (1973). Magnification was constant in each case (× 1.3) and allowance was made for this in the subsequent assessment. Lateral and postero-anterior tomography was performed in each case. All the pneumoencephalograms have been reviewed by one of us (I.G.W.), without reference either to the original radiological reports or to the clinical findings.

Atrophy of the cerebellar vermis, based on the criterion that sulci of 2 mm or less were normal, was assessed in the sagittal tomogram. Atrophy was graded as mild (+), moderate (++) or severe (+++), and its distribution was described as generalized or focal. Examples of these distinctions are illustrated in Figs. 1–4. Apparently excessive prominence of the primary cerebellar fissure was regarded as a variation of the normal appearance. The half-axial, postero-anterior projection was used to assess atrophy of the cerebellar hemispheres as present if air was demonstrated on their superior surfaces, or absent if it was not. No attempt was made to quantify this observation further. The fourth ventricle was enlarged in all planes of measurement (Amundsen and Grimsrud, 1966; Robertson, 1967) in all the cases studied but this feature was not separately assessed. The presence and severity of any associated cerebral atrophy was noted and graded on a scale of mild (+), moderate (++), and severe (+++).

Finally, the overall severity of cerebellar atrophy was assessed in each case, taking into account atrophy of the vermis and hemispheres, widening of the vallecula, size of the fourth ventricle and enlargement of the cisterna magna and other subarachnoid cisterns. These additional features enabled us to rank the 44 patients in sequential order according to the degree of overall cerebellar atrophy in each. This rank order was used for statistical analysis. Line drawings were made from tracings of the midline tomograms in the sagittal plane and these were used for comparison between cases.

Clinical assessment. Each of the 44 patients had been examined by an experienced neurologist or neurosurgeon. In those few cases in which there was doubt about a particular clinical feature one of us (P.K. or M.S.) has re-examined the patient. In most cases the findings of more than one observer were available for comparison and this facilitated uniformity of judgement from case to case in our retrospective assessment.

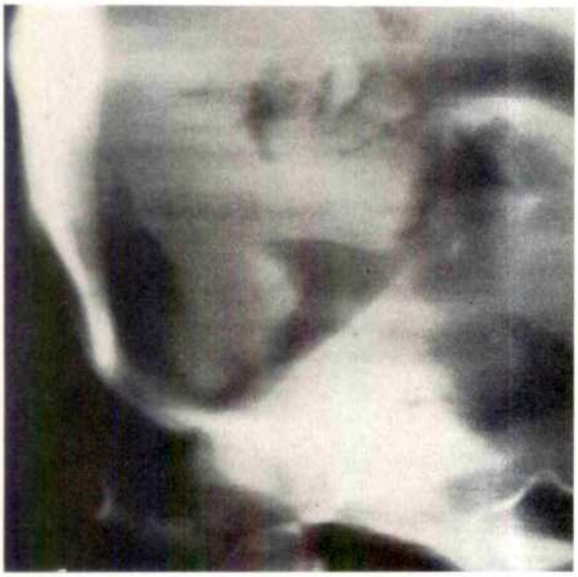

FIG. 1.

Pneumotomogram in sagittal plane. Mild atrophy of the anterior vermis.

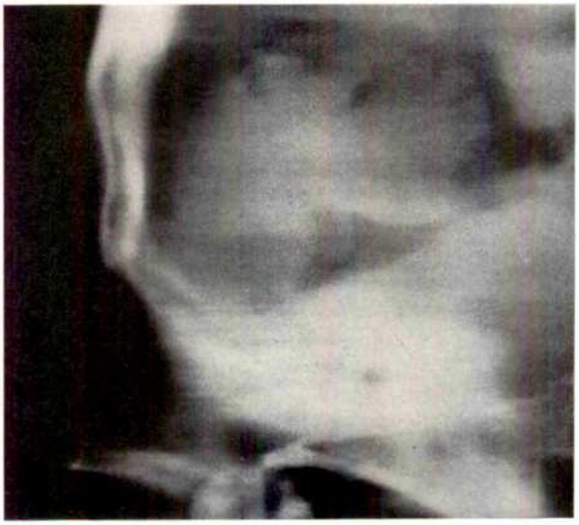

FIG. 2.

Pneumotomogram in sagittal plane. Moderate atrophy of the anterior vermis.

Particular attention was paid to the presence or absence of ataxia of gait, limb ataxia, titubation, nystagmus, dysarthria and hypotonia, but no weighting was given to any of these signs. Each, if present, was graded as mild (+), moderate (++) or severe (+++). Addition of these individual scores allowed the accumulation of a total score for each case (maximum 18). These scores were made without knowledge of the radiological findings.

Indications for pneumoencephalography. Some of the 44 patients were under the care of physicians or surgeons in other departments of the hospital. This has led to the inclusion of patients with a wide variety of diagnoses; some, indeed without a pathologically-based diagnosis. For example, a number of cases (see Tables V and VI) have been categorized as Ménière's syndrome, or vertigo. In these patients pneumoencephalography was performed because it was thought, on otological criteria, that their symptoms might be due to acoustic Schwannoma, a tumour of particular interest in this hospital (Morrison and King, 1973). In each case the diagnosis given was considered by us, in retrospect, to be the most appropriate in relation to all the available clinical data.

Two patients in the series have since died, and autopsies were performed in both (see Table III).

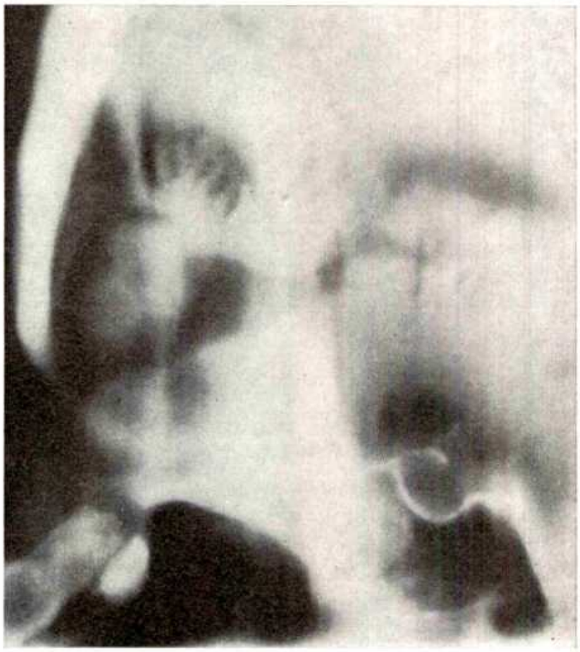

FIG. 3.

Pneumotomogram in sagittal plane. Moderate generalized atrophy of the vermis.

RESULTS

The clinical and radiological data are summarized in Tables III, IV, V and VI.

Radiological data

Atrophy of the cerebellar vermis was present in 43 of the 44 patients and atrophy of the cerebellar hemispheres in 12. In one patient (case 43) there was atrophy of the cerebellar hemispheres without associated atrophy of the vermis.

TABLE I

GENERALIZED VERMIS ATROPHY (33 PATIENTS)

Severity	No. of patients	Clinical score	
		Mean	Range
Mild	17	1	0–6
Moderate	14	3	0–10
Severe	2	0	—

TABLE II

ANTERIOR VERMIS ATROPHY (10 PATIENTS)

Severity	No. of patients	Clinical score	
		Mean	Range
Mild	6	0	0–1
Moderate	4	6	0–10
Severe	—	—	—

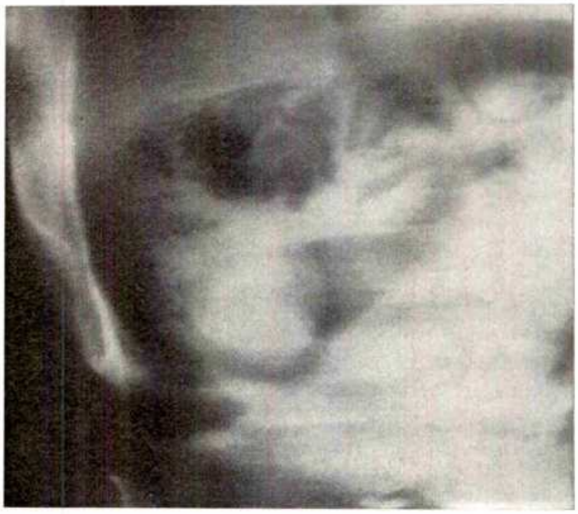

FIG. 4.

Pneumotomogram in sagittal plane. Severe generalized atrophy of the vermis.

TABLE III

Patients with cerebellar signs

Case	Diagnosis	Age	Clinical features						Score	Cerebellar atrophy		Cerebral atrophy
			Gait ataxia	Limb ataxia	Titu-bation	Dys-arthria	Nystag-mus	Hypo-tonia		Vermis	Hemi-sphere	
1	Spinocerebellar degeneration	45	2	2					4	++generalized		+++
2		53	1	3					6	+generalized		+
3		56	2	2		1			5	generalized		++
4		74	2	1		1	1		5	++anterior		+
5	Alcoholic cerebellar	43	3	2	1	2		1	9	++generalized	+	++
6		73	2	3		1	1		7	++anterior		++
7	Brain stem infarction	54	3	1					4	++generalized		++
8	Brain stem infarction	72	2	2		1	2		7	++generalized		
9	Cerebral vascular disease	55					1		1	+generalized	+	+++
10	SBE cerebral infarct meningitis	59	1						1	+generalized		++
11	Phenytoin induced cerebellar degeneration	33	2	3	1	1	2	1	10	++generalized	+	
12	CA cerebellar degeneration*	59	3	3	1	1	1	1	10	++anterior		+
13	Multiple sclerosis	52	1	1			1	1	4	+generalized	+	
14	?Pseudo tumour cerebri*	63	1						1	++generalized		++
15	Brain stem syndrome	65		1		1	1		3	++generalized	+	+
16	? Post. fossa tumour	82		1			1		2	++generalized		

*Autopsy available. +mild ++moderate +++severe

TABLE IV

Patients with moderate cerebellar atrophy: no cerebellar signs

Case	Diagnosis	Age	Cerebellar atrophy		Cerebral atrophy
			Vermis	Hemisphere	
17	Old cerebellar atrocytoma	34	++generalized	+	
18	Cerebrovascular disease	52	++generalized		+
19	Ménières disease alcoholism	53	++generalized		+
20	Steele-Richardson syndrome	56	++anterior		+
21	Pseudotumour cerebri	58	++generalized	+	++
22	Cerebrovascular disease	63	+++generalized		+++

+mild ++moderate +++severe

Vermis atrophy. In 33 patients there was atrophy of the whole vermis, in ten it was confined to the anterior vermis, and in one patient there was no atrophy of the vermis. In the 33 patients with generalized atrophy of the vermis, comparison of the severity of the pneumographic atrophy and the mean clinical score suggests that this radiological finding, when considered alone, has little practical significance in diagnosis (Table I). Neither of the two patients with severe atrophy of the vermis had associated atrophy of the cerebellar hemispheres.

In the ten patients in whom atrophy was restricted to the anterior part of the vermis there was a more clearly defined correlation between the radiological and clinical findings (Table II). Cerebellar signs were present in three of the four patients with moderate atrophy (cases 4, 6 and 12), but in none of the six patients with only mild atrophy (cases 24, 25, 31, 32, 34 and 37).

Hemisphere atrophy. Atrophy of the cerebellar hemispheres (Tables III, IV and VI) was present in only 12 patients (29%). In 11 of these the atrophy

TABLE V

PATIENTS WITH MILD CEREBELLAR ATROPHY: NO CEREBELLAR SIGNS

Case	Diagnosis	Age	Cerebellar atrophy		Cerebral atrophy
			Vermis	Hemisphere	
23	Vertigo	31	+ generalized		
24	TLE	37	+ anterior		+
25	Post-traumatic encephalopathy	40	+ anterior		
26	Vertigo	48	+ generalized		
27	Hodgkin's disease (intracranial)	54	+ generalized		+
28	Cerebral metastasis	55	+ generalized		
29	Steele-Richardson syndrome	62	+ generalized		+
30	Vertigo	63	+ generalized		++
31	Sphenoid meningioma meningitis alcoholism	65	+ anterior		+++
32	Cerebral infarction	74	+ anterior		+

+ mild ++ moderate +++ severe

TABLE VI

CEREBELLAR ATROPHY IN PATIENTS WITH DEMENTIA

Case	Age	Cerebellar signs	Cerebellar atrophy		Cerebral atrophy
			Vermis	Hemisphere	
33	55	1	+ generalized	+	++
34	58	0	+ generalized		
35	58	0	+ anterior	+	+++
36	59	0	+ generalized		+
37	60	1	+ anterior		++
38	61	0	+ generalized		+
39	64	0	+ generalized		+
40	66	0	++ generalized	+	++
41	68	1	++ generalized		++
42	68	0	+++ generalized		++
43	72	1		+	++
44	76	3	+ generalized	+	+

+ mild ++ moderate +++ severe

was graded as mild. In one patient who had had surgery to the cerebellum there was moderate hemisphere atrophy. In 11 of these 12 patients the vermis was also atrophic: in ten, atrophy of the vermis was generalized, and in one it was focal. In six patients the associated atrophy of the vermis was of moderate severity and in five vermis atrophy was assessed as mild. Cerebellar signs were present in eight of the 12 patients in whom there was atrophy of the cerebellar hemispheres, including one patient (case 43) in whom the vermis was normal.

The mean clinical score in the 12 patients with atrophy of the cerebellar hemispheres was 3 (range 0–10). It is clear that atrophy of the anterior vermis was more closely related to the clinical score than atrophy of the cerebellar hemispheres.

Cerebral atrophy. Cerebral atrophy was present in 34 patients (71%). The presence and severity of cerebral atrophy showed no correlation with the clinical scores. Similarly, there was no correlation between cerebral and cerebellar atrophy when the cases were ranked according to overall severity of cerebellar atrophy (Kendall's rank correlation test). Cerebral atrophy was most severe in the patients with spinocerebellar degeneration, alcoholism, cerebro-vascular disease, and dementia.

Clinical Data

Cerebellar signs, of varying severity, were observed in 21 of the 44 patients. Sixteen of these are shown in Table III: the remaining five were investigated by pneumoencephalography because of dementia and these are included in Table VI. In four of these five patients (cases 33, 37, 41 and 43) the "cerebellar" signs consisted only of slight unsteadiness of gait, a feature which is difficult to assess in patients with dementia. The other (case 44) was thought to have sustained a brain stem infarct some years before the onset of a progressive dementia.

The ages of the 16 patients with cerebellar signs included in Table III ranged from 33 to 82 years (mean 59 years). The clinical scores ranged from one to ten. In all except two (cases 10 and 14) the cerebellar signs could clearly be related to the clinical diagnosis and in both these cases the cerebellar signs consisted only of a slight abnormality of gait. This was, perhaps, particularly questionable in case 14 in whom the final clinical diagnosis was benign intracranial hypertension. By far the most striking of the clinical signs was ataxia of gait and of limbs, which was present in *all* those patients whose clinical score was greater than three. Indeed in several patients these were the only clinical features of cerebellar disease observed.

The 23 patients without cerebellar signs are described briefly in Tables IV, V and VI. Of the 16 patients (age range 31 to 74 years: mean age 53 years) with mild or moderate cerebellar atrophy (Tables IV and V), but without clinical signs of cerebellar disease, 11 had associated cerebral atrophy. This was no more frequent or severe in those with moderate cerebellar atrophy than in those in whom cerebellar atrophy was mild. Atrophy of the cerebellar hemispheres was present in only two of the 16 patients and in one of these (case 17) there had been previous cerebellar surgery. In most of these patients (cases 20–23 and 26–30) there was no evident clinical explanation for the pneumographic cerebellar atrophy.

Twelve patients with dementia were found to have cerebellar atrophy (Table VI). Their ages ranged from 55 to 76 years (mean 60 years). Atrophy of the vermis was present in all but one (case 43), in whom there was atrophy of the cerebellar hemispheres alone. In one patient (case 34) mild generalized atrophy of the vermis was present without associated cerebral atrophy. The severity of the cerebellar atrophy in these patients (Table VI) could not be directly correlated with the severity of the cerebral atrophy. The ataxia found in five of these patients has been discussed above.

Overall statistical assessment of radiological/clinical correlation

Kendall's rank correlation test (Siegel, 1956) was applied to the radiological and clinical data derived from *all* the patients. The 44 cases were ranked according to an *overall* assessment of the severity of the pneumographic cerebellar atrophy, using all the parameters described above, and this ranking was compared with the clinical scores of cerebellar signs. There was a significant relationship between the two ranks of data at the 5% level ($p=0.0516$). When cases without clinical signs of cerebellar disease were omitted from the rankings, leaving only 21 cases (Tables III and VI), correlation between pneumographic cerebellar atrophy and clinical scores became significant at the 3% level ($p=0.0307$). No correlation was found between the occurrence of cerebellar signs and increasing age.

Neuropathological correlation

Cases 12 and 14, both of whom had moderately severe pneumographic cerebellar atrophy, died and came to autopsy. In case 12 these was no pathological evidence of cerebellar atrophy. The size and pattern of the cerebellar folia and sulci was normal. In this case there were pronounced histological changes in the cerebellum, brain stem and spinal cord. These consisted of degeneration and loss of Purkinje cells and of cells in the granular layer of the cerebellum, and also of neuronal loss in the dentate and olivary nuclei. Neuronophagia was seen in these nuclei. Scattered perivascular cuffing with mononuclear inflammatory cells was present in the lower brain stem and cerebellum; and there was slight pallor of the posterior columns. There was mild cerebral atrophy with slight ventricular enlargement. These changes were consistent with those described in previously reported cases of the cerebellar syndrome associated with neoplasms (Brain and Wilkinson, 1965), in which an associated encephalomyelitis may rarely occur.

In case 14 the cerebellum and brain stem were normal, both macroscopically and microscopically. The lateral ventricles were of normal size and there was no cerebral atrophy.

DISCUSSION

In the whole population of 44 cases, there was a significant correlation between the severity of the clinical signs of cerebellar disease and the degree of pneumographic cerebellar atrophy ($p=0.0516$). This relationship was even closer ($p=0.0307$) when only those patients with cerebellar signs were studied. Nonetheless, there were no clinical signs of cerebellar disease in 23 of the 44 patients. In a number of these patients (Tables IV, V and VI) there was no clinical suspicion of cerebellar disease and pneumographic cerebellar atrophy was an unexpected finding for which there was no ready explanation. It is, of course, possible that in these patients cerebellar atrophy had developed slowly allowing time for functional compensation to occur. This must have been a factor in some patients, as in case 34, in whom a cerebellar astrocytoma had been resected some years previously, but in the majority this seems an unlikely explanation. An alternative possibility is that the criteria we have used for assessment of cerebellar atrophy were incorrect and that mild atrophy of the cerebellar vermis, for example, was merely a variation of the normal. We consider the latter suggestion unlikely since our criteria were more stringent than those used by others, and we have been able to demonstrate a rank-order correlation between the radiological and the clinical data in our 44 cases.

There have been several previous attempts to correlate radiologically demonstrated cerebellar atrophy with clinical signs of cerebellar disease. In all these studies (Uzman, 1948; LeMay and Abramowicz, 1966; Castorina and Opice, 1966; Strecker *et al.*, 1972) it has been observed that apparently advanced cerebellar atrophy was not necessarily associated with clinical signs of cerebellar disease, although Thiébaut *et al.* (1966), whose study was limited to cases with pneumographic atrophy of the vermis, found ataxia of gait in nearly all their patients. Momose *et al.* (1971), for example, using an assessment based on increased width of cerebellar sulci and a simple graded score of the amount of air pooled over the superior borders of the cerebellar hemispheres, found cerebellar atrophy in 23 of 31 patients with Cushing's disease, but there were no clinical signs of cerebellar disease in any of their patients. These disparities can probably be accounted for by the differing indications for pneumoencephalography in these various studies, by variations in the criteria used for assessment of cerebellar atrophy, and by differences in pneumoencephalographic technique.

In a number of previous studies it has been suggested that enlargement of the prepontine and quadrigeminal plate cisterns, and of the cisterna magna and 4th ventricle, might be useful criteria of cerebellar atrophy (Uzman, 1948; Robertson, 1967; Bentson and Alberti, 1972; Strecker *et al.*, 1972), but although these abnormalities were present in most of our patients they were of no apparent clinical value, when considered alone, particularly in relation to the presence or absence of clinical signs of cerebellar disease. For example, these abnormalities were all present to an advanced degree, together with atrophy of the cerebellar vermis and hemispheres, in case 9, a patient in whom a permanent cerebellar syndrome seemed to have resulted from prolonged phenytoin overdosage, but a similar abnormality was present in several other patients in whom there was no clinical evidence of cerebellar disease.

In our experience the most reliable part of the pneumoencephalographic assessment of cerebellar atrophy has been the mid-line tomogram in the sagittal plane, which delineates the folial pattern of the vermis, the height of the 4th ventricle, and the size of the brain stem, the subarachnoid cisterns of the pons, quadrigeminal plate, vallecula and cisterna magna in a single film (Figs. 1–4). This sectional plane is particularly useful because it is often used in the pathological assessment of cerebellar atrophy, as by Victor *et al.* (1959) in their study of cerebellar cortical degeneration in alcoholism. Atrophy of the vermis correlated well (Tables I and II) with clinical signs of cerebellar disease in our patients, and this was also the experience of Thiébaut *et al.* (1966). Atrophy of the cerebellar hemispheres, on the other hand, could not easily be correlated with signs of cerebellar disease; although it was found in some patients with recognized disease of the cerebellum (Table III) it was also found in some patients without evident cerebellar disease (Tables IV, V and VI).

In all our patients two or more cerebellar sulci exceeded 2 mm in width. Thus all had cerebellar atrophy of at least "mild to moderate" severity according to the criteria of LeMay and Abramowicz (1966). We have therefore defined the "mild to moderate" group of LeMay and Abramowicz as mild atrophy, and their "severe" group as moderate atrophy. However, since there were differences in pneumographic technique between our study (Morris and Wylie, 1973) and those of LeMay and Abramowicz (1965; 1966), especially concerning the use of lateral and postero-anterior tomography, careful control of anaesthesia, and of the rate and volume of injection of subarachnoid gas, the two studies may not be strictly comparable. It is particularly striking, despite the overall statistical relationship, that there were no clinical signs of cerebellar disease in many of our patients with mild cerebellar atrophy (Tables V and VI), and in some of those with moderate atrophy (Table IV). LeMay and Abramowicz (1966) also observed this disparity between the clinical and radiological data.

The cerebellum was studied at autopsy in two of our patients (cases 12 and 14) but in neither was there macroscopic evidence of cerebellar atrophy in the sagittal section of the vermis, although in both these cases the pneumotomogram of the same region was thought to show atrophy of moderate severity

(Fig. 2). The pathological criteria for cerebellar atrophy rest on the macroscopic appearance of decreased folial thickness and increased sulcal width, but the folial pattern in a fixed specimen may not accurately reflect the appearances demonstrated during pneumoencephalography. For example, it has been shown that ventricular size may increase during the course of a single pneumoencephalographic examination (Lim *et al.*, 1972) and this observation introduces doubt about the reproducibility of measurements of sulcal size during pneumoencephalography. For the pathologist, furthermore, the size of the subarachnoid spaces, for example the size of the space between the superior surfaces of the cerebellar hemispheres and the tentorium cerebelli, is a theoretical rather than a practical entity. It is difficult, therefore, to compare radiological and neuropathological assessments of cerebellar atrophy even in the same patient.

The twelve patients with dementia, thought by exclusion to be due to Alzheimer's disease, formed the largest diagnostic category in our series. The predominance of these cases occurred because at the time of the study patients with dementia formed the largest group undergoing pneumoencephalography. Further, the patients with dementia in our study (Table VI) were selected because they were found to have pneumographic cerebellar atrophy. In only three of these patients, however, was the pneumographic cerebellar atrophy more than mild. It is clear from Roessman's (1974) work, our own autopsy experience, and our inability to find a correlation between cerebral and cerebellar atrophy in the whole group of 44 cases, that there is no direct relation between cerebral and cerebellar atrophy. Nonetheless Gawler *et al.* (1976), using computerized axial tomography, found atrophy of cerebellar sulci in 17 of 26 patients with cerebral atrophy.

This problem has been approached somewhat differently by Roessman (1974) who has studied the weight of the cerebellum and brain stem, expressed as a percentage of the total brain weight. In fourteen cases of Alzheimer's disease (Roessman, 1974) this ratio was 13.7%, a figure significantly different from the normal ratio of 12.45% ($p<0.01$). It was concluded from this work that the cerebellum and brain stem do not undergo atrophy to the same extent as the cerebral hemispheres in Alzheimer's disease. Ellis (1920) stated that the weight of the human cerebellum decreases between the third and ninth decades by 8% in men and 7% in women, and that most of this reduction in weight occurs after the age of 50 years. Blinkov and Glezer (1968) thought that this loss of weight was accompanied by a reduction in the length of the cerebellar hemispheres. Roessman did not list the actual weights of the infratentorial structures in his paper (Roessman, 1974). Hall *et al.* (1975) have recently confirmed earlier suggestions that loss of Purkinje cells occurs with increasing age in man and have found that this trend becomes marked only after the age of 60 years. We found no correlation between pneumographic cerebellar atrophy and increasing age in our patients.

Although we have been able to show a correlation between the various radiological parameters we have studied and the clinical scores, particularly in the instance of atrophy of the anterior vermis, no single radiological parameter proved an invariable index of clinically apparent cerebellar disease. Overall assessment, based on a simple visual inspection of all the films from each case, together with measurement of sulcal width in the sagittal pneumotomogram of the anterior vermis, proved fairly reliable, as was shown by our statistical analysis of the correlation between clinical signs of cerebellar disease and pneumographic cerebellar atrophy, but the finding of unexpected cerebellar atrophy in some patients (Tables IV, V and VI) makes radiological assessment meaningless in individual cases, unless accompanied by clinical information. In future studies computerized axial tomography may be helpful (see Gawler *et al.*, 1976) particularly because the problem of artefactual variability in sulcal size can be excluded with this technique.

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We thank Professor H. Urich for the neuropathological work.

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Book review

Myelography. By Robert Shapiro, pp. 602, 594 figs., 3rd edn. 1975 (Published by Yearbook Medical Publishers Incorporated. Distributed in U.K. and Europe by Lloyd Luke (Medical Books) Ltd, London), £23·40.

This book is now probably the best known standard text on the neuroradiological examination of the spinal canal. The third edition maintains the high standard of its predecessors, being well written and beautifully produced with carefully chosen illustrations and diagrams. In addition to the general revision of the book there are several important new chapters.

Professor Djindian summarizes the value of spinal angiography in a short chapter supplemented by a well selected bibliography.

Professor M. Roth contributes a chapter on pneumomyelography, stressing its value in the diagnosis of syringomyelia, atrophy and thoracic disc protrusion. It is, perhaps, unfortunate that the technique described is one for simple apparatus, and utilizes tomography on a horizontal table. In this country it will usually be performed in centres with specialized apparatus allowing more exactly controlled techniques to be used.

Professor F. P. Gargano discusses lumbar epidural venography. Cervical epidural venography is not considered. The author's technique of injecting directly into the ascending lumbar veins, is not, in the reviewer's experience, as reliable as more selective catheterization. The application of the method to the diagnosis of lumbar disc lesions is fully discussed but its value in the diagnosis of sacral lesions is not considered.

It is unfortunate that the water soluble myelographic contrast agent Metrizamide had not been more extensively discussed in the literature prior to the drafting of this edition. There is no doubt that it will lead to considerable modification in the practice of myelography and will hopefully stimulate an early fourth edition of this outstanding book.

B. KENDALL.

1976, *British Journal of Radiology*, *49*, 912–920

Quantitative radiology: radiogrammetry of cortical bone

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ABSTRACT

Based on personal experience and data in the literature, an overview is given of radiogrammetry of cortical bone of the second metacarpal. There is a within- and between-observer error which amounts respectively to 1.2 and 1.5% for the outer diameter and 4.8 and 6.4% for the inner diameter. The systematic + or − trend between observers indicates that one observer working according to certain defined rules obtains the most reliable results.

There is a large variability in amount of bone within one age and sex group which is partly due to skeletal size differences. The relative indices which were introduced to correct skeletal size differences, are insufficient since skeletal size differences still exist. The variability is reduced when the data are divided into strata of skeletal size. Since cortical area shows the best correlation with outer diameter within each age group and since cortical area represents best the ash content of the bones the values of this index are most suited to be grouped according to outer diameter. In differentiating pathological from physiological bone loss this procedure is an improvement on the previously published indices of amount of bone. When comparing different populations this method has advantages since skeletal size differences are eliminated. Comparing seven populations it was found that populations living in the United States of America have more bone for a given skeletal size than populations in Europe or Nigeria.

Bone loss with age is a general phenomenon but differences in rate of loss are observed between the sexes and between ethnic different populations. The decrease of bone mass is faster after the age of 50 years in woman than in men. Blacks living in the United States loose less bone with age than whites.

Radiogrammetry of cortical bone in groups gives useful information on bone remodelling during ageing and in pathological conditions. At an individual level, however, it it is difficult to evaluate changes on a short term basis with radiogrammetry.

Radiogrammetry of cortical bone is a simple and reproducible method which measures bone mass indirectly. Changes in cortical width show a high degree of correlation with the changes in mass of cortical bones but trabecular bone is not measured. This is a serious handicap, since most of the metabolic diseases of the skeleton affect trabecular bone to a greater extent than cortical. Nevertheless the measurement of cortical thickness certainly has added to the knowledge of changes in bone mass in ageing and in disease.

The introduction of a simple radiogrammetric evaluation of cortical bone thickness in long bones simultaneously by Virtama and Mähönen (1960) in Finland and Barnett and Nordin (1960) in Great Britain and two years later by Meema (1962) in Canada, brought quantitative radiology in the field of clinical practice and epidemiology.

Since radiogrammetry of cortical bone at the second metacarpal has now been in practice for 15 years it is intended to give an overview of this technique based on our own experiences and reports from other centres.

MEASURING TECHNIQUE

Measurements are made from postero-anterior hand radiographs taken at a uniform 1 m tube-to-film distance, using non-screen film. Morphometric measurements are performed at the midshaft of the right second metacarpal. The length (L) of the second metacarpal of the right hand is measured with a millimetre rule. The midshaft of the metacarpal is found by dividing the length and a pencil mark is drawn at right-angles to the long bone axis as illustrated in Fig. 1. The Leeds group (Horsman and Simpson, 1975), however, defines the mid-shaft with respect to the metaphysis. Since the Leeds group make their measurements at another point, which is more proximal, their data will not be exactly comparable to the date of Bugyi (1965); Dequeker (1972); Exton-Smith *et al.* (1969b); Garn *et al.* (1967b); Gryfe *et al.* (1971); and Virtama and Helelä (1969).

The basic measurements are the outer diameter of periosteal width (D) and the inner diameter or medullary space (d) of the cortex at the midpoint of the shaft at right angle on the long axis. The measurements are best made to 0.1 mm with a direct reading needle-tipped Vernier caliper. The use of a rule is less accurate. Since the thickness of the cortex and the diameter of the metacarpal, on average, are smaller in the left hand than in the right (Adams *et al.*, 1969; Dequeker, 1972), some metacarpal should always be measured. Most authors use the right metacarpal.

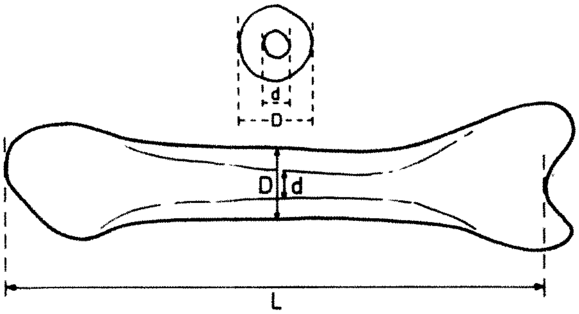

FIG. 1.

Outline of metacarpal bone, showing measurements made from radiographs.

MEASURING ERROR

The mean difference between observers for the outer diameter was found to be 1.5% and for the inner diameter 6.4% of the overall mean value (Dequeker, 1972). There was a systematic + or — difference in the values obtained by different observers. Virtama and Helelä (1969) also found a systematic + or — trend in the values obtained by different observers. Adams *et al.* (1969), using calipers and a ruler to 0.5 mm, reported a maximum difference between observers and within observers for cortical thickness of respectively 8.3 and 8.6%. Virtama and Helelä (1969) found an inter-observer error varying from 4.5 to 5.8%.

Because the inter-observer error depends partially on the difficulty in defining the exact margins of the cortical layer, especially the inner margin, it is advisable to stick to certain basic principles when cortical measurements are made. The inner limit of the cortical layer must be defined as the border of the solid cortical layer without separate trabeculae in the vicinity of the inner border as advised by Virtama and Helelä (1969). The need for more than one observer in measuring the cortical layer as proposed by Adams *et al.* (1969) is open to question. On the contrary the systematic + or — trend between observers give reason to believe that one observer working according to certain defined rules obtains the most reliable results.

INDICES OF BONE MASS–INFLUENCE OF SKELETAL SIZE

Cortical thickness can be calculated by simple subtraction of medullary width (d) from metacarpal width (D) (D—d).

Since the second metacarpal is approximately circular at midshaft and the medullary cavity is nearly centred in the tubular bone cylinder at that point, calculation of cross-sectional area is feasible. The total and medullary cross-sectional areas can therefore be calculated, and the cortical area is taken as the difference between these two values. Omitting the constant $\pi/4$, D^2, d^2, $D^2—d^2$ can be regarded as an index of total cross-sectional area, medullary cross-sectional area and cortical cross-sectional area.

Various values of relative amount of bone were derived from the basic measurements D and d: the Barnett–Nordin metacarpal index (Barnett and Nordin, 1960) which is the percent ratio of cortical thickness of the metacarpal to the total width of the bone D-d/D%; the percent ratio cortical area to total area D^2-d^2/D^2%; and the ratio cortical area to surface area as described by Exton-Smith *et al.* (1969a) $D^2-d^2/D.L.$

The multiplicity of indices proposed indicates that none has been really satisfactory. Within one sex/age group there is considerable variability, which makes differentiation between normal and abnormal difficult. The variability is most probably due to heterogeneity of skeletal size (Dequeker, 1970b). The effect of skeletal size (outer diameter) on indices of bone mass is shown in Table I. The values d and L are computed from the regression of inner diameter (d) and length (L) on outer diameter (D) in the age group 25–34 years (Dequeker, 1972). The age group 25–34 years was chosen because at this age women and men attain maximum amount of bone. The correction introduced by relating cortical thickness to outer diameter as Hossain *et al.* (1970) suggested, or by relating cortical area to surface area as Exton-Smith *et al.* (1969a) proposed is incomplete. When these relative indices were introduced it was assumed that the ratio compact bone/total bone would be the same for different sizes of bones and that variations in body size would in this way be corrected. In mechanics, however, it is well known that resistance of tubular structures to flexion can be maintained with a lower wall-area/total area ratio provided that the total diameter of the tube is large (Smith and Walker, 1964). While cortical thickness, cortical area and cortical area/surface area ratio increase, % cortical thickness and % cortical area/total area decrease with increasing outer diameter.

Recently Morgan (1973) introduced a complex index, the cross sectional cortical area corrected to a standard size of bone (CA_C). This index is based on the assumption that there is little correlation between

TABLE I

INDICES OF BONE MASS FOR DIFFERENT SIZES OF SECOND METACARPAL BONE AT MIDPOINT IN THE AGE GROUP 25–34 YEARS.

L	D	d	D-d	$\frac{D\text{-}d\%}{D}$	D^2-d^2	$\frac{D^2\text{-}d^2}{D^2}$	$\frac{D^2\text{-}d^2}{D.L.}$
				Females			
6.10	7.0	2.20	4.80	68.57	44.16	90.12	0.1034
6.30	8.0	2.80	5.20	65.00	56.16	87.75	0.1114
6.55	9.0	3.45	5.55	61.66	69.10	85.30	0.1172
				Males			
6.80	8.0	3.35	4.65	58.12	52.78	82.46	0.0970
7.00	9.0	3.85	5.15	57.22	66.18	81.70	0.1050
7.25	10.0	4.40	5.60	56.00	80.64	80.64	0.1112

L = length; D = outer diameter; d = inner diameter; D–d = cortical thickness; D–d/D = % cortical thickness; D^2–d^2 = cortical area; D^2–d^2/D^2 = % cortical area /total area; D^2–$d^2/D.L.$ = cortical area/surface area.

cortical thickness and the width of the shaft in healthy persons aged 20–40 years. As shown above this is not the case in our series and in the series of Adams *et al.* (1969) where a significant correlation was found. Morgan, furthermore, concluded that his corrected cortical area (CA_C) gives identical information to the simple cortical thickness index.

Relation Between Peripheral and Axial Bone Mass

There is a good statistical relationship between the bone mass of the peripheral and axial skeleton; between metacarpal bone and stature (Dequeker *et al.*, 1969); between cortical thickness and spinal porosity grades (Meema, 1963; Saville, 1967; Dequeker *et al.*, 1971a); between cortical thickness and fat-free bone weight per unit volume of iliac crest biopsies (Saville and Nilsson, 1966; Dequeker *et al.*, 1971b).

Although the correlations between peripheral and axial skeletons are significant, less than 40% of the variation is accounted for in the regression (Doyle, 1972). This observation indicates that a knowledge of the amount of bone in one particular bone is of little help in predicting fractures in other parts of the skeleton. Adams *et al.* (1970) have shown that measurements of metacarpal thickness in surveys 11 years apart, or of change in thickness between the surveys, were of no value in selecting the people who sustained peripheral or vertebral fractures.

Morgan (1973), however, questions the conclusion of Adams *et al.* (1970) on the grounds that the measuring error, due to the use of calipers and a ruler, could have accounted for the major part of the observed variation in rate of bone loss.

Normal Values

Cross-sectional data on measurement of bone mass in normal adult populations reported by different authors show the same pattern. All indices show an increase up to the age of 30–40 years, followed by a progressive decrease, which is far more pronounced in women (Fig. 2). The decrease is faster after the age of 50 years in women. Males exceed females in absolute amount of bone (cortical thickness and cortical area), throughout the age range 15–80 years. The relative amount of cortical bone is greater in females up to the sixth decade. With advancing age and more rapid bone loss associated with age in females, the male/female ratio of relative bone mass is reversed. Thus individual or group data have to be compared with data from controls matched for age and sex. Nordin *et al.* (1970), however, suggest that as a reference normal value, the mean value of the cortical area/total area ratio of young people should be taken as the "bone standard". Doing so they fail to take into account the distribution of normal data and also fail to incorporate an age or sex correction. Consequently nearly all people above the age of 60 will have an abnormal low value. This advice has not been followed by most authors.

The difficulty of differentiating pathological from physiological bone loss is linked to the large variability of bone mass within one age-group. This variability in bone mass is almost constant and not influenced by age or sex and amounts to ±15% for cortical thickness, ±17% for cortical area, ±10% for percent cortical area and ±11% for cortical area/surface area. As shown previously this variability is partly due to heterogeneity of skeletal size. Therefore the variability should be reduced when the data are divided into strata of skeletal size. Since cortical area (D^2-d^2) shows the best correlation with outer diameter (D) within each age group (Dequeker, 1972) and since cortical area represents best the ash content of the bone (Exton-Smith *et al.*, 1969a), the values of this index are most suited to be grouped according to outer diameter. The results of this procedure are shown in Fig. 3. For each skeletal size group a distinct and significant amount of bone (cortical area) per age and sex group could be established with a low S.D. When these calculations were compared with the data obtained for all skeletal size groups taken together, the mean S.D. for males was reduced from 10.3 to 6.3 for females from 9.1 to 5.5. At age 35 there are no sex differences in amount of bone for the same skeletal size. So women start at age 35 with as much bone as men for the same skeletal size, but their loss is far more pronounced with advancing age.

In differentiating pathological from physiological bone loss this procedure is an improvement on the previously published indices of amount of bone (Dequeker, 1970a). When comparing different populations this method has advantages since skeletal size differences are eliminated.

Table II shows the difference of skeletal size and its influence on cortical area at age 40 of seven populations; three ethnically different populations from the United States of America (black, white and Mexican (data from Garn *et al.*)); three European populations (Dutch, Belgian (Dequeker, 1972) and Finnish (Virtama and Helelä, 1969)); and one African population (Nigeria (Dequeker, 1972)). When the data of these seven populations based on 12007 hand X rays are statistically analysed an international normative trend line corrected for skeletal size

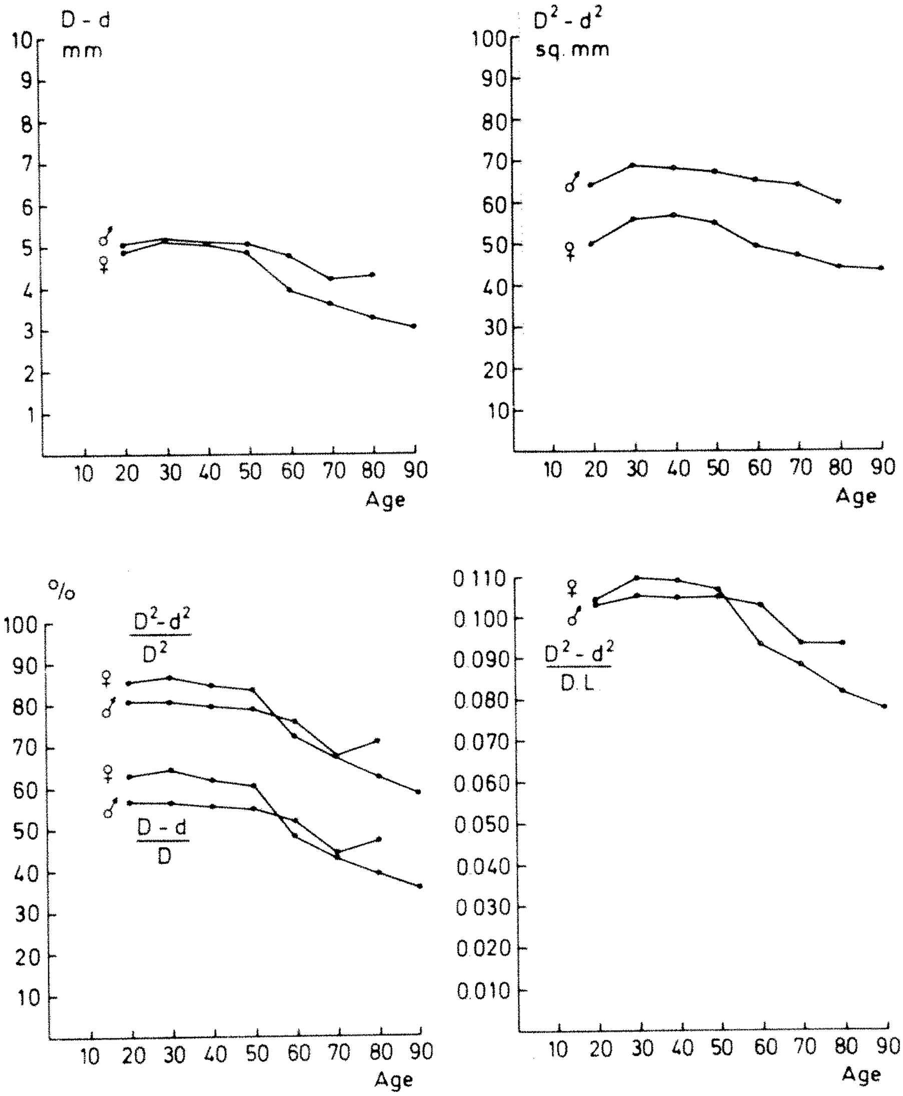

FIG. 2.

Age-associated changes in indices of amount of bone calculated from measurements made at midpoint of the second metacarpal in 643 women and 194 men from Belgium.

(outer diameter) can be obtained (Dequeker, unpublished data). This study discloses interesting population differences in bone mass of the metacarpal (Table III). In general, populations living in the United States of America have more bone for a given skeletal size than populations in Europe or Nigeria.

In conclusion it may be stated that to make valid comparisons between the bones of different individuals, different sexes and different populations variations in skeletal size, age and sex must be taken into account.

Since there are variations in skeletal size and in amount of bone for a given skeletal size between populations, normal values have to be established for each population separately.

BONE REMODELLING AND AGEING

Throughout life, even after cessation of longitudinal growth, cancellous and cortical bone are constantly being replaced by resorption of existing areas and by production of new deposits in microscopical amounts at many sites heterogeneously distributed throughout the skeleton. Changes in this

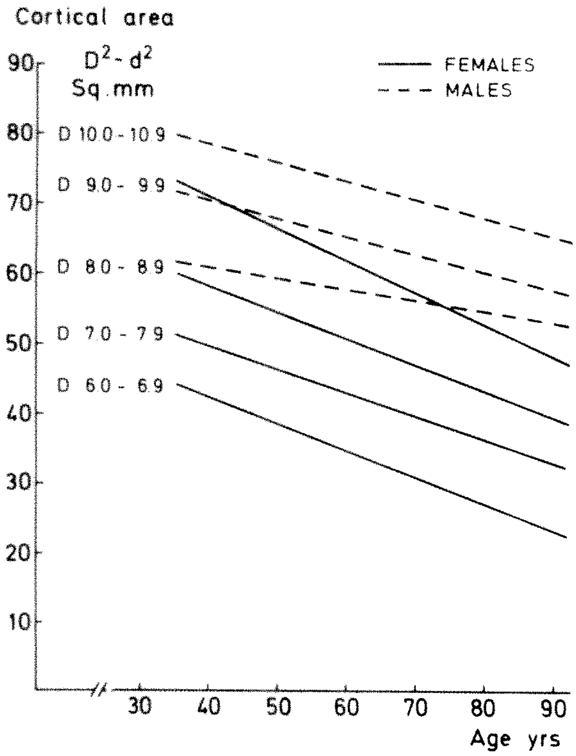

FIG. 3.

Regression of cortical area on age according to skeletal size (D) of the second metacarpal at midpoint in Belgium women and men.

TABLE II

COMPARISON OF MEAN PERIOSTEAL DIAMETER (D) AND MEAN CORTICAL AREA (D^2–d^2) IN SEVEN POPULATIONS AT AGE 40

	Females		Males	
	D	D^2–d^2	D	D^2–d^2
Dutch	8.67	64.38	9.62	73.93
USA black	8.51	61.51	9.92	82.00
Finland	8.40	60.95	9.60	76.95
USA white	8.08	58.11	9.51	77.90
Belgium	8.17	56.94	9.25	68.10
Nigeria	7.90	52.24	8.88	64.67
USA Mexican	7.22	54.20	8.28	70.45

TABLE III

% DIFFERENCE CORTICAL AREA FROM INTERNATIONAL TREND LINE SKELETAL SIZE ADJUSTED, AT AGE 40 AND AT AGE 80 OF SEVEN POPULATIONS

	Females		Males	
	Age 40	Age 80	Age 40	Age 80
USA Mexican	+3.7	+6.0	+4.4	+6.4
USA white	+2.9	+5.3	+3.5	+2.0
Finnish	+2.0	−2.8	+1.8	+2.3
USA black	+1.3	+6.6	+0.9	+2.0
Belgium	−1.7	−5.9	−4.3	−10.0
Dutch	−1.9	−1.9	−4.2	−2.2
Nigerian	−6.4	−7.3	−2.2	−0.6

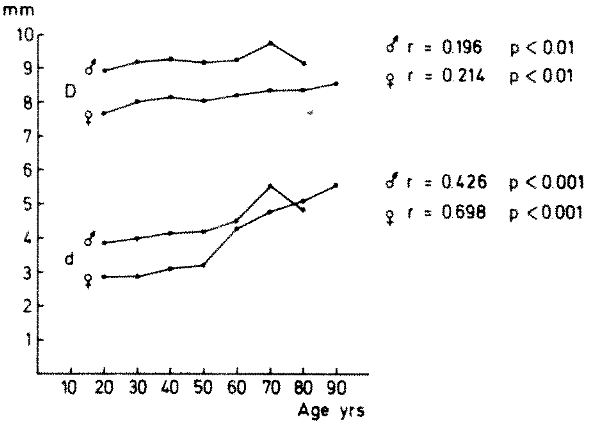

FIG. 4.

Age-associated changes in periosteal (D) and endosteal (d) diameter of the second metacarpal at midpoint in 643 women and 194 men.

balance between formation and resorption have a critical role in calcium homoestasis and underlie every disease with a notable influence on the adult skeleton (Harris and Heaney, 1969a). X-ray determination of periosteal and endosteal surface changes in long bones in different populations or in the same population over a period of time provides information on skeletal dynamics. Skeletal renewal at the second metacarpal during ageing is shown in Fig. 4 (Dequeker, 1972a). The periosteal and endosteal diameters increase significantly with age in both sexes. The observed increase in periosteal diameter confirms the large-scale cross-sectional findings reported by Bugyi (1965); Virtama and Helelä (1969); Garn *et al.* (1967a); and Adams *et al.* (1970). The latter authors were able to exclude selective survival or a secular trend on the basis of longitudinal data on older adults followed over 15-year and an 11-year period, respectively. Smith and Frame (1965), however, did not observe a significant increase in metacarpal periosteal diameter in 2063 women, age range 45 to 90 years. It is also unlikely that periosteal bone growth is a compensatory response to endosteal bone loss, as the rate of periosteal growth is not necessarily in proportion to the rate of endosteal loss (Garn and Poznanski, 1970).

As both processes may represent responses to different mechanical and hormonal stimuli, they have to be considered separately in studies of osteoporosis and osteoporotic bone loss.

Medullary cavity expansion due to endosteal bone loss is characteristic of advancing age in both sexes. Though medullary expansion rates and the endosteal bone losses are relatively low in the fourth and the fifth decade, expansion in both sexes increases after the age of 50, more so in women than in men. The endosteal surface enlarges throughout life faster than the periosteal surface, causing a net loss of cortical bone. Thus bone loss with age is not the result of decreased bone formation but the result of a lack of balance between formation and resorption.

BONE REMODELLING IN PATHOLOGICAL CONDITIONS VERSUS BONE REMODELLING IN AGEING

Bone involution seems to be a general phenomenon and a normal manifestation of the atrophy of tissues in the process of ageing. The rarer occurrence of osteoporosis in other diseases, particularly those involving hormonal disturbances, and also in younger people for no apparent reason, is of great interest. Since these conditions cannot be attributed to normal ageing, they may provide clues to the nature of the osteopenia in older people. Since the major metacarpal bone dimensions—total subperiosteal width, medullary cavity width, and cortical area—can be measured on X-ray films, it is possible to base skeletal remodelling distinction on these dimensions and compare them with the norms and standards for an individual of that age, sex and race.

Table IV compares the bone remodelling processes in pathological conditions with those in normal ageing (Dequeker, 1971; Roh *et al.*, 1973). Bone remodelling and bone mass in female patients suffering from idiopathic vertebral collapse did not differ significantly from controls matched for age and sex. A significant increase in endosteal bone loss was seen in cases with femoral neck fracture, with disuse osteoporosis of hemiplegia, with rheumatoid arthritis (anatomical stage III–IV), with corticosteroid-treated rheumatoid arthritis, stage II, with primary hyperparathyroidism, and with Turner's syndrome. A significant difference between bone formation and resorption was seen in pre- and post-menopausal hyperparathyroid women. In the latter an imbalance between bone formation and resorption with cortical bone loss was observed (Dequeker, 1972).

Periosteal bone loss has been noted in a case with idiopathic osteoporosis and in a case with amputated fingers. A significant increase in periosteal bone gain occurred in cases with primary hyperparathyroidism, acromegaly, and primary osteoarthrosis.

The observation of increased bone mass measured by radiography (Foss and Byers, 1972; Roh *et al.*, 1973) and confirmed by photon absorptiometry (Roh *et al.*, 1974) at the forearm is of particular interest since osteoarthrosis is a common affection occurring in the older age group. Thus in old people there seems to be a wide range. At one end are light-boned osteoporotic women without osteoarthrosis who suffer fractures. At the other end are individuals with strong bones without fractures who suffer from osteoarthrosis (Dequeker *et al.*, 1975).

Using the normative trend line on age for outer and inner diameter and cortical area, the influence of drugs on skeletal remodelling can be studied. The long-term effect of oestrogens on bone remodelling is shown in Fig. 5. Forty-six post-menopausal women were treated with conjugated oestrogens 1.25 mg or ethinyloestradiol 0.025 mg. daily. The normal trend lines are derived from measurements of a control population of 643 women. The outer diameter, which represents the bone apposition parameter, is not significantly greater than in the control group but the inner diameter, which represents the bone resorption parameter is significantly smaller than the control group. Bone remodelling in oestrogen-treated post-menopausal women differs from normal controls matched for age and sex by a lower endosteal bone resorption rate resulting in a significantly larger bone mass than untreated control subjects (Dequeker and Ferin, 1976).

LIMITS OF THE RADIOGRAMMETRIC APPROACH

Although radiogrammetry of the second metacarpal has been found useful in epidemiologic studies of ageing phenomena, in comparing bone remodelling in pathological conditions and in establishing the effect of treatment in groups of patients, it has failed to give information on the bone status at an individual level due to the large variability in each sex-age group even when it is corrected for skeletal size (Dequeker, 1975 and Dequeker *et al.*, 1975).

On an individual and short-term basis the static radiographic picture does not necessarily coincide with direct measurements of bone dynamics. Over a period of time, however, the two must of necessity agree. What is measured by radiogrammetry is not long-term gain at the outer bone surface and net long term loss/gain at the inner bone surface. It is the balance of the bone bank that it is reported, not the statement of deposit or withdrawal that occurs daily.

TABLE IV

REMODELLING PROCESSES AT THE PERIOSTEAL AND ENDOSTEAL SURFACE OF THE SECOND METACARPAL IN DIFFERENT CONDITIONS

Condition	Periosteal surface	Endosteal surface	Cortical area
Ageing	Bone gain	Bone loss	Decrease
Femoral neck fracture	Bone gain	Bone loss +	Decrease +
Vertebral collapse	Bone gain	Bone loss	Decrease
Idiopathic osteoporosis	Bone loss + +	Bone loss	Decrease + + +
Hemiplegia	Bone gain +	Bone loss +	Decrease
Rheumatoid arthritis (RA) Stage III–IV*	Bone gain	Bone loss + + +	Decrease + +
RA + corticosteroid	Bone gain O	Bone loss + +	Decrease + +
Amputation	Bone loss	Bone loss	Decrease + +
Hyperparathyroidism	Bone gain +	Bone loss +	Normal or decrease
Turner's syndrome	Bone gain	Bone loss + +	Decrease + +
Acromegaly	Bone gain +	Bone loss or gain	Increase
Osteoarthrosis	Bone gain +	Bone loss	Increase

*Steinbroker (1949).
†Indicates the difference with the remodelling process in normal ageing.

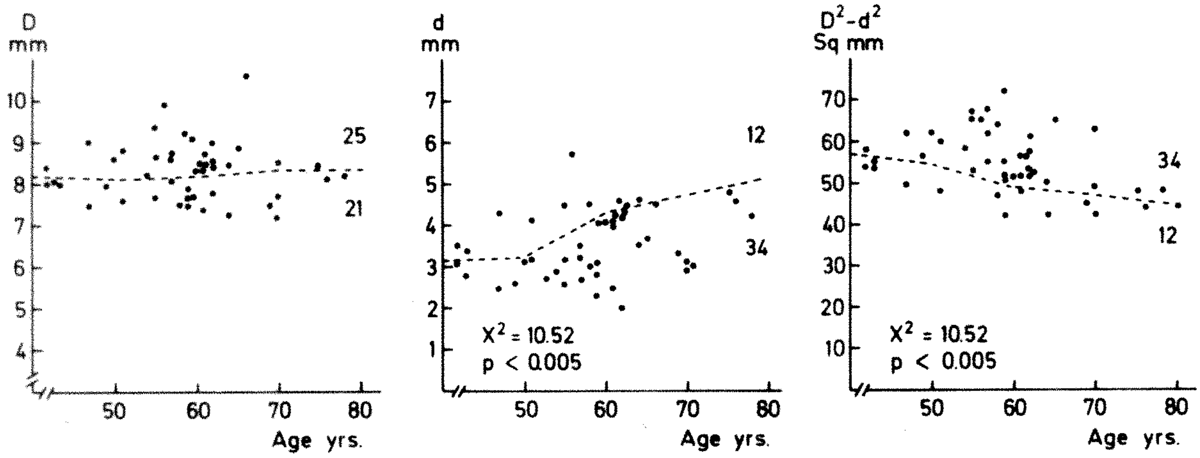

FIG. 5.

Effect of oestrogen treatment on bone remodelling in 46 post-menopausal women.

From cross-sectional studies we know that the average loss in women is about 0.9% and in men 0.4% per year in the age range 40–80 years. Knowing that the measuring error may amount to 8% for cortical thickness it is clear that an interval of many years is necessary to find a longitudinal difference in a normal ageing individual with certainty. As a group, however, statistically significant differences may be found compared with a control group after two to five years depending on the size of the groups.

In order to monitor longitudinal studies attempts to improve the precision of the technique, especially to relocate the same measuring site on consecutive X-rays, are under study. Recently Horsman and Simpson (1975) published an elaborate method for evaluation of sequential changes occurring in the thickness of the cortices. The method utilizes pairs of hand radiographs from which the total bone width and medullary width of the 2nd, 3rd and 4th metacarpals are determined in duplicate using needle-tipped Vernier calipers. Changes in cortical width of ± 1.5% could be detected with ± 95% confidence. A mean rate of decrease of cortical width in normal post-menopausal women of ± 0.04

mm/year was observed. Thus a significant reduction in cortical width will be detected in such women in less than two years.

Another limitation of the radiogrammetry method is the occurrence of local disorders of bone as occur after fracture of the bone in the neighbourhood or in rheumatoid arthritis.

There may also be a permeative type of cortical bone loss which may be apparent on observation (Meema and Schatz, 1970), but which effects the cortical measurement only slightly. This phenomenon is seen in thyrotoxicosis and with rapid bone loss such as occurs in some cases of immobilization or disuse, particularly in the initial phase.

A serious limitation of radiogrammetry of cortical bone is that it does not measure trabecular bone. Most of the metabolic diseases of the skeleton affect trabecular bone to a greater extent than cortical. Nevertheless, the measurement of cortical bone certainly has added to the knowledge of changes in bone mass in ageing and in disease.

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Book review

A Textbook of Radiology. Edited by David Sutton, 2nd edn, pp. xiii + 1,376, 1975 (Edinburgh, London and New York, Churchill Livingstone), £25.

There are those who believe that a single-volume text-book has no place in a wide-ranging subject such as radiology. Certainly there are problems; every section is inevitably compressed, and it is not easy to give an adequate picture of individual disease processes. There are also difficult decisions on which conditions or procedures to mention, particularly when the aim is, as the author's foreword indicates, to be both comprehensive and concise. Yet the success of the first edition of this book shows that Dr. Sutton was right in his belief that there was a need for such a work, and after being out of print for two years the second edition has already enjoyed a wide scale. It is not difficult to see why; anyone who has worked towards an examination such as the D.M.R.D. will know the value of having a source of basic information giving him a core of knowledge on which to build. In simple economic terms too, there is much to be said for a single book which will cover all the needs of the radiologist in training.

The question then is, Does the book succeed in its own terms—is it authoritative, is it comprehensive and yet concise? On the whole it is, but there are aspects which leave room for improvement. One persistent failing lies in the layout. Again and again the illustrations are some way, often pages distant, from the point where they are mentioned in the text. This can admittedly be difficult for the publishers, but one has the impression at times that they are unaware that the problem exists, and do not realize just how exasperating it can be to read a book in which one is for ever thumbing backwards or forwards between text and picture. The publishers are also badly at fault in the reproduction of some radiographs. Fortunately, most of the contributors recognize the need to show only as much of a radiograph as is necessary, so that in general even poorly reproduced figures still convey their message. However, in the section on breast disease (too short a section incidentally) the reproduction of the figures is of unacceptable quality, and justice has not been done to what were presumably good illustrations. There are times too when the authors are at fault in not remembering the junior level of their readership. A number of figures could well have been supplied either with an arrow to indicate the lesion in question or an example of a normal to help point out the abnormality.

A major problem in a book of this sort is to achieve an appropriate balance, each section taking the reader to approximately the same level of complexity. Broadly, the level is about right, in examination terms the book should carry its readers comfortably through the D.M.R.D., but leave them well short of the F.R.C.R. Some parts, however, are distinctly tougher, notably the excellent sections on heart disease and the C.N.S. On the other hand, too little has been made of nuclear medicine, and ultrasound is hardly mentioned. Another point which arises in a comprehensive text-book is where to put the accounts of conditions which can be considered in more than one section. There are some lapses in this regard. The reader can find a discussion of spondylolisthesis both in the section on bones and joints, and also in that on the spine which is part of the nervous system. Myostitis ossificans is mentioned both under bones and joints, and again in the section on soft tissues, and in one section a short first metatarsal is shown, in the other a short first metacarpal. Both the section on bones and that on chests illustrates sarcoid of the hand, an unimportant condition, and one which should not be given this kind of emphasis.

Inevitably, there are a number of points where there is room for disagreement on what should have been included. For example, needle lung biopsy and bronchial brushing in the diagnosis of lung masses are surely worth a mention. Under communicating hydrocephalus the use of radionuclide cystography is not discussed. With the increasing immigrant population it is surprising that description of primary tuberculosis does not include presentation with bilateral mediastinal glands in some adult patients. And while the section on skull fractures includes paragraphs on aeroceles and pneumocephalus, it does not point out that the potential significance of sphenoid air fluid levels in indicating a probable fractured base. In addition to questions of omission, there are sections which are incomplete. There is very little on the important and common problem of distinguishing ulcerative colitis and Crohn's colitis. The point is discussed, rather oddly, in the chapter on the small bowel, and the table comparing the two conditions dates from 1960. Hirschsprung's disease is, if not common, an important diagnosis, and it is a pity that it is only illustrated by a diagram while the text gives no indication of the variation in extent of the condition, nor is it made clear that preparatory washouts should not normally be used. Examples of the misleading or inaccurate are harder to find, but it is wrong to suggest that Lipiodol is now used in the diagnosis of oesophageal atresia. Equally, it is sad to find the expression "dye" used for contrast medium in a radiological textbook (page 816), and I am not the only radiologist to dislike the term "lung markings".

Of course reviewers generally feel obliged to make such comments, and it is true that most of the book is sound and well balanced, and that it has much to offer its readers. Nevertheless, it does represent British radiology to the world, and it is a pity that it should be flawed in any way, particularly by the publisher's inadequacy. All in all then, a good book, well worth owning, but still not realizing its full potential.

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Bone demineralization in renal failure: a longitudinal study of the distal femur using photon absorptiometry

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ABSTRACT

The bone mineral content (BMC) of the lower end of the femur was measured by photon absorptiometry in 87 patients with chronic renal failure. The γ-ray photon source was Am^{241}. Serial measurements were obtained for up to two years. The mean BMC of the adult patients, comprising: 18 pre-dialysis (CRF), 41 chronic haemodialysis (CHD) and 19 renal transplant (RT) patients were all significantly lower than controls with the exception of the male CRF group. Two adults and one child on chronic haemodialysis showed a significant rate of bone loss ($> 2\%$ per year). In one of these adults the addition of daily oral 1 α hydroxycholecalciferol was associated with no further reduction in BMC. Two children and one adult on chronic haemodialysis showed a significant rate of increase in BMC ($> 2\%$ per year). This adult had had a tendency to loss of BMC on standard CHD treatment but after receiving parenteral 1,25 dihydroxycholecalciferol three times weekly showed a significant rate of increase in BMC. No CRF or RT patient had a significant rate of loss of BMC on serial measurement. Two adults and one child with CRF had a significant rate of increase in BMC on standard treatment.

Progressive bone demineralization is a well-documented complication of chronic renal disease (David, 1970). Routine radiological evaluation of skeletal status is of limited value for patient management in this condition since it is commonly found that some 30 to 50% of bone mineral must be lost before signs of bone demineralization appear on standard X rays (Lachman, 1955; Meema and Meema, 1963). Recently developed photon absorptiometry techniques provide the accuracy and sensitivity required for clinically useful measurements of bone mineral content (BMC); changes in BMC between 2 to 4% can be readily detected (Cameron *et al.*, 1968).

The usual sites for measurement of BMC by photon absorptiometry are the lower radius and ulna. In chronic haemodialysis patients, however, the rate of change in BMC obtained at these sites has a low degree of correlation with the rate of change of BMC in other areas of the body (Dalen and Alvestrand, 1973), with progressive pathological changes in the iliac crest (Cordy *et al.*, 1974), or with changes in the calcium content of the hand as measured by neutron activation analysis (Catto *et al.*, 1973). In addition, serial measurements of change in BMC at the lower radius and ulna of patients with chronic renal failure have produced variable results even in the same centre; in some patients, BMC increased, in some it decreased, and in some it remained the same (Catto *et al.*, 1973; Ringe *et al.*, 1974; Schuster, 1974; Griffiths *et al.*, 1973; Meema *et al.*, 1970).

Measurements of mineral content in chronic renal failure have also been made for the os calcis (Banzer and Schneider, 1974; Banzer *et al.*, 1974) and distal femur (Atkinson *et al.*, 1970; Atkinson *et al.*, 1973); the results were similar to those obtained for the radius/ulna.

Using a measurement apparatus constructed in this laboratory (Overton *et al.*, 1974), with Am^{241} as the photon source, we studied BMC in the distal femur of 87 chronic renal failure patients comprising; 21 pre-dialysis patients (CRF), 45 chronic haemodialysis patients (CHD), and 21 renal transplant patients (RT).

METHODS

Bone mineral content measurements are made for all patients referred to the renal unit at the University of Alberta Hospital.

Patient selection for inclusion in this report was based upon the availability of at least five BMC measurements for all patients in each group.

Volunteers, aged 18–68 years, with no history of diseases involving bone metabolism, provided the "normal" data for this study. These consisted of 60 women and 63 men (Table 1).

Pre-dialysis patients (serum creatinine 3 to 14 mg%) and CHD patients received 0.125 mg dihydrotachysterol (Hytakerol^{R}) twice daily and sufficient aluminium hydroxide in either the liquid or tablet form to maintain a normal serum phosphorus concentration. Two CHD patients received 0.5 to 2 μg of 1,25 dihydroxycholecalciferol (1,25 DHCC) parenterally three times weekly while on

TABLE I

Mean BMC (g/cm) at distal femur site for normal and renal disease groups

FEMALES						
Normal Group			(Number in group)* Mean BMC g/cm			
Age (years) mean ± sd range	Height (cm)	Weight (kg)	Normal	CRF	CHD	RT
31.7 ± 18.4 18–68	165 ± 6	58.3 ± 7.8	(60) 3.54 ± 0.48	(9) 3.17 ± 0.64	(13) 3.15 ± 0.75	(9) 2.98 ± 0.72
MALES						
29.1 ± 11.3 19–68	178 ± 7	72.4 ± 9.7	(63) 4.59 ± 0.74	(9) 4.23 ± 0.68	(28) 4.11 ± 0.99	(10) 4.04 ± 0.71

*Excluding nine children (seven females, two males)

dialysis, and two received 0.5 to 2 μg daily of oral 1 α hydroxycholecalciferol (1 α HCC).

Chronic haemodialysis patients received dialysis for three to eight hours, two to three times weekly. The dialysis fluid was fluoride-free; it had a calcium concentration of 6.5 mg% and a magnesium concentration of 1.5 mg%. Either 17 micron Gambro Lundia or Model 4 Cordis Dow dialysers were used. The diet was restricted in salt and water as necessary and had a protein content of 1 to 1.25 g/kg body weight per day.

Patients who received a renal transplant were treated with Prednisone and Azathioprine in the following doses: Prednisone, 100 mg daily, commencing immediately following surgery. This dosage was reduced gradually, during a three month period, to 20 mg daily at which level it was maintained for most patients.

Azathioprine, average 1.5 mg/kg body weight with a range 0.5 to 3.0 mg/kg body weight.

Bone mineral content measurements were made in the distal femur at a site approximately one fifth of the shaft length from the lateral tubercle. Measurements were made at about two month intervals over an average period of 12 months (range 8 to 24 months).

Group comparisons of mean BMC using a 2-tailed "t" test were made after determining that no significant differences existed in age, height or weight between groups. For the longitudinal study a weighted linear regression (BMC *v.* Time in days) was made for eight normals (five males, three females, each with a minimum of five measurements in the study period) and for each individual patient. In all cases the slope of the regression line was tested for a difference from zero slope. In the reported cases where patients changed groups or type of treatment a comparison was also made between the regression slopes before and after the change.

We used data obtained in long-term studies of BMC measurement precision to define a BMC "trend" threshold in terms of the slope of the regression line BMC *v.* Time for normal subjects. This threshold value was 0.0005 g/cm/day which corresponds to a rate of change in BMC between 1 and 2% per year depending upon the particular group (normal or patient) considered.

RESULTS

Mean BMC values for male and female "normal" groups and for males and females with renal disease are shown in Table I. In all BMC comparisons each patient group had a lower value than the normal group. This difference was significant ($p<0.01$) with the exception of the male CRF group. Bone mineral content comparisons between the three patient groups showed no significant differences.

During this study significant ($p<0.05$) BMC increases were found in five patients (Table II). Three of these five patients, however, were children aged 11 to 14 years, and the increase in BMC was attributed to normal growth during the study period. Two CHD patients (one adult and one child) showed significant loss of BMC during this study ($p<0.05$). A test of proportions (Table II) comparing each group for positive *v.* zero and negative trends showed that the patient groups were significantly different from normal ($p<0.05$) but not from each other.

Six patients (included in Table II) underwent a therapy change during the period of this study (4 CRF→CHD, 1 CHD and 1 CRF→RT). No change in BMC was observed following this therapy change.

TABLE II

NUMBERS OF SUBJECTS WITH CHANGE IN BMC FOR NORMAL AND RENAL DISEASE GROUPS

		Normal	CRF	CHD	RT
Total number in group*		8	26	42	21
BMC increase		0	3 (1 child)	2 (children)	0
BMC decrease		0	0	2 (1 child)	0
TREND	Positive	0	5	9	6
	Zero	8	13	18	7
	Negative	0	5	11	8

*Includes nine children and six patients with therapy change (5 CRF → 4 CHD + 1 RT; 1 CHD → 1 RT)
Excludes four CHD patients with special therapy (two receiving 1,25 DHCC and two receiving 1αHCC)

Results for four additional CHD patients (not included in Table II), two who received 1,25 DHCC and two who received 1αHCC, are shown in Table III. One of the two who received 1,25 DHCC showed a negative trend in BMC before receiving the drug and a significant increase in BMC during treatment (Silverberg *et al.*, 1975); the other showed a zero trend before and during treatment. One of the two who received 1αHCC showed a significant loss of BMC before receiving the drug and a zero trend during treatment; the other showed a zero trend before and during treatment.

Mean values for serum calcium, phosphorus, and alkaline phosphatase for the CHD patients included in Table II are shown in Table IV. Mean serum alkaline phosphatase and phosphorus values were significantly higher than normal ($p < 0.01$), but no significant changes in these values were seen for any of these patients during the study period.

Radiological skeletal surveys were performed prior to and at the termination of this study; no evidence of change in bone demineralization was observed for any patient included in the CRF, CHD or RT groups (Table II). In patient No. 1 (Table III) who received 1,25 DHCC there was radiological evidence of improvement in osteitis fibrosa and osteomalacia, and in patient No. 3, who received 1αHCC, there was radiological evidence of healing of fractures of two metatarsal bones during treatment. In both patients the serum alkaline phosphatase fell significantly during the treatment with these vitamin D analogs.

DISCUSSION

In this study, by measuring the distal femur, we found the mean BMC for CRF, CHD and RT patients to be significantly lower than normal. Similar observations have also been made for the distal radius and/or ulna in CRF (Ringe *et al.*, 1974; Schuster, 1974; Griffiths *et al.*, 1973; Meema *et al.*, 1970), CHD (Ringe *et al.*, 1974; Griffiths *et al.*, 1973; Meema *et al.*, 1970; Stewart *et al.*, 1973; Boyd *et al.*, 1974; Lindergard *et al.*, 1972), RT (Griffiths *et al.*, 1973), and for the os calcis in CRF, CHD and RT (Banzer and Schneider, 1974; Banzer *et al.*, 1974).

On the other hand, when taking measurements over a period of up to 24 months, we found no change in BMC in any of the three groups tested, or in any patient transferred from one group to the other. In our study group of 87 patients only two individuals, one adult and one child (CHD), showed a significant rate of BMC loss; five individuals, two adults and one child (CRF) and two children (CHD), showed a significant rate of BMC gain. These findings contrast with the results of other centres which have measured the distal radius and/or ulna of patients and reported that the majority demonstrated BMC loss during the measurement period. This was true for CRF (Griffiths *et al.*, 1973; Meema *et al.*, 1970), CHD (Catto *et al.*, 1973; Ringe *et al.*, 1974; Meema *et al.*, 1970), and RT (Griffiths *et al.*, 1973; Meema *et al.*, 1970). In CHD and RT patients measurements of the os calcis have provided similar results (Banzer and Schneider, 1974; Banzer *et al.*, 1974). Atkinson *et al.* (1973) measured the distal femur and found that BMC decreased in all six patients on chronic peritoneal dialysis over a 40 week period, though in a two and one half year follow-up, only one of two showed continuing BMC loss. The study also reported decreases in six of seven patients on CHD over a 40 week period, but in a 36 month follow-up only three of five of these patients continued to show bone loss; of the two others, one showed no change, and one showed an increase in BMC. Two patients on CHD received renal transplants and both experienced a greater rate of loss of BMC after transplantation than before; one of these patients, however, had a transplant that functioned poorly.

Our results also contrast with those of Dalen and Alvestrand (1973) who measured BMC in CHD and RT patients at several different sites in the body using X-ray spectrophotometry. The mean BMC of all CHD and RT patients was found to be significantly lower than normal and a loss in BMC, with time, occurred in both groups. Measuring the shaft of the femur in 16 CHD patients, a mean BMC loss of 2.3% during an average of ten months was found; in 12 RT patients, a mean BMC loss of 1.7% over a two to four month period was reported.

TABLE III

RATE OF CHANGE IN BMC IN FOUR CHD PATIENTS RECEIVING VITAMIN D ANALOGS

CHD patient	Drug	Duration of study (days)		Number of measurements		Linear regression analysis BMC *v.* Time (days)		
						Slope g/cm/d		Comparison of slopes
		Before R_x	During R_x	Before R_x	During R_x	Before R_x	During R_x	Before R_x/During R_x
1 m	1,25 DHCC	79	556	6	13	−0.0012	+0.0013*	significant difference $p < 0.001$
2 f	1,25 DHCC	94	298	5	5	−0.0001	−0.0003	not significant
3 m	1αHCC	140	446	4	7	−0.0009*	−0	significant difference $p < 0.001$
4 f	1αHCC	347	162	5	3	−0.0001	−0	not significant

*Significant difference from zero slope $p < 0.05$

TABLE IV

MEAN VALUES FOR ALKALINE PHOSPHATASE, CALCIUM AND PHOSPHORUS IN 44 CHD PATIENTS DURING THE STUDY PERIOD. CHD PATIENT GROUP

	Mean ± SE	Average number of measurements	Normal range
Alkaline phosphatase IU/L	137 ± 35	16	20–90
Calcium mg%	9.6 ± 0.15	14	8.5–10.5
Phosphorus mg%	6.0 ± 0.29	15	2.5–4.5

Why have we found no change in BMC in any of our patient groups, whereas most other authors report that loss of BMC occurs whether the measurement site is the distal radius and/or ulna, the os calcis, or the distal femur or shaft? There are several possible explanations.

All our CRF and CHD patients were on Hytakerol^R, a vitamin D analog which aids calcium absorption, thus helping to prevent hyperparathyroidism (Kaye *et al.*, 1970). In CRF patients, vitamin D supplementation has been associated with an increase in BMC (Schuster, 1974); in CHD patients such supplementation has been associated with progressive loss of bone in some cases (Atkinson *et al.*, 1970; Atkinson *et al.*, 1973). In our study, however, and in that of Cordy *et al.* (1974), supplementation with Hytakerol^R in CHD patients has been associated with no change in BMC.

The reported relationship between dialysate calcium and change in BMC is variable. Progressive loss of BMC has been seen in the majority of patients by workers who used dialysate calcium concentrations of 5.3 to 5.5 (Catto *et al.*, 1973), 6.0 to 6.2 (Atkinson *et al.*, 1970; Atkinson *et al.*, 1973), and 6.4 mg% (Dalen and Alvestrand, 1973), but not by others who used dialysate calciums of 6.0 (Kaye, 1973), 6.2 to 6.4 (Cordy *et al.*, 1974), 6.5 (our study), and 8 mg% (Ringe *et al.*, 1974). Dialysate calcium concentrations above 6.0 mg% have been associated with a positive calcium balance during dialysis (Wing, 1968).

The reported relationship between fluoride in the dialysate and changes in BMC is also inconsistent. In some studies in which the dialysate contained fluoride, loss of BMC was noted in the majority of cases (Meema *et al.*, 1970), whereas in other studies no change in BMC was found (Cordy *et al.*, 1974). In our study, fluoride was removed from the dialysate.

Control of serum phosphate concentration using aluminium hydroxide is important in preventing secondary hyperparathyroidism, since a high serum phosphate inhibits renal production of 1,25 DHCC, the agent responsible for calcium absorption from the gut (DeLuca, 1975). However, the reported relationship between serum phosphate and change in BMC has been variable. In CHD patients, a loss of BMC has been noted when serum phosphate concentrations were 4.2 (Atkinson *et al.*, 1973) and 5.4 mg% (Dalen and Alvestrand, 1973), but in other studies with values of 4.8 (Kaye, 1973), 5.4 (Cordy *et al.*, 1974), and (our study) 6.0 mg%, no loss of BMC occurred.

The stable values of BMC obtained during the two-year period of our study showed a high degree of correlation with other measured parameters. No significant change in alkaline phosphatase was observed in the chronic haemodialysis group, and there was no change in the degree of mineralization on the usual skeletal X rays. If bone loss in the distal femur did occur, the rate of loss was less than 2% per year. This beneficial result may be related to the use of Hytakerol^R, fluoride-free dialysate, a dialysate calcium concentration sufficient to create a positive calcium balance, and to the control of hyperphosphataemia.

The only adult who showed an increase in BMC during chronic haemodialysis treatment was one of the two patients receiving parenteral 1,25 DHCC. Prior to treatment this patient showed a trend to BMC loss. One of the two CHD patients who received 1αHCC, and who prior to this treatment experienced significant bone loss, had no additional loss of BMC during treatment. The changes in BMC in these two patients (No. 1 and No. 3 in Table III) were associated with radiological evidence of bone improvement and a fall in serum alkaline phosphatase. Others have also shown improvement in renal osteodystrophy with these agents (Brickmann *et al.*, 1974; Chalmers *et al.*, 1973).

Serial BMC measurements at a distal femur site have been made for normal volunteers and for patients with renal disease during a two-year period. This BMC measurement technique, with a long-term precision of better than 2%, permits early detection of bone mineral loss and is, we believe, a valuable method in following renal osteodystrophy.

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Effect of Crohn's disease on colonic diverticula

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ABSTRACT

Fifteen cases in which the same part of the colon has been affected by both diverticular disease and Crohn's disease have been studied. When Crohn's disease affects an area of colon where diverticula are present, radiological examination may show a diminution in number or disappearance of the diverticula with progress of the Crohn's disease. With improvement in the Crohn's disease diverticula may appear.

Colonic diverticulosis is most often seen after the age of 50. Crohn's disease of the colon occurs not infrequently in the same age-group, so their occasional association is to be expected. Indeed, Crohn's disease affecting the distal colon has been observed to be particulary common in the elderly (Lockhart-Mummery, 1972). The differentiation between Crohn's disease and diverticular disease, or the recognition that both are present, is clearly of vital importance in reaching decisions regarding treatment and may at times cause considerable difficulty (Schmidt *et al.*, 1968; Marshak *et al.*, 1970). The object of this study is to draw attention to a point of relevance to this problem. It has been observed that a length of colon found to be involved with diverticular disease on radiological examination may later show no diverticula, or a reduced number, when the same area is subsequently affected by Crohn's disease. Conversely, when Crohn's disease has improved, the appearance of diverticula has been noted.

CLINICAL MATERIAL

Fifteen cases, in whom diverticular disease and Crohn's disease affected the same segment of colon, have been studied. There were four men and 11 women. Their ages ranged from 47 to 80 with a mean of 67. All except two were over 60.

Apart from clinical and radiological evidence, the presence of Crohn's disease was established by a positive rectal biopsy with granulomata in seven. In two cases the rectal biopsy showed non-specific inflammatory changes, but the radiological picture was typical of Crohn's disease. Pathological examination of colectomy specimens in four further cases gave unequivocal evidence, while in another post-mortem examination later confirmed granulomatous colitis. There was one patient who had been treated with azathioprine, where histological examination of the excised colon left the distinction between ulcerative colitis and Crohn's disease in doubt. However, previous radiology had shown a long stricture with a communicating intramural sinus, rose-thorn ulcers and a recto-vaginal fistula.

Of the four men, three had disease confined to the distal colon and rectum. In the fourth the distal colon was involved when the patient was first seen, but subsequently the disease spread to involve the whole colon and terminal ileum. Of the 11 women one had involvement of most of the colon and terminal ileum, two had a total colitis, four had left-sided colitis and four a distal colitis. Seven of the 11 women had anal lesions and two of the four men, but their presence was not correlated with the severity of the disease.

The duration of the disease at the time the first barium enema was carried out was relatively brief, being six weeks or less in eight of the cases while the others had had symptoms for varying intervals up to 18 months.

RESULTS

Two of the patients had only one barium enema performed and are included for the sake of completeness. The remaining 13 cases had more than one examination and these can be divided into four groups:

(A) *No change in the diverticula* when the Crohn's disease spread to involve the part of the bowel where the diverticula were situated—two cases.

(B) *The diverticula diminished in number* when the Crohn's disease involved the segment of the bowel previously affected by diverticula—six cases.

(C) *The diverticula disappeared completely* when the affected part of the bowel became involved with Crohn's disease—three cases. In one of these patients the diverticula subsequently reappeared when the Crohn's disease had become quiescent following a defunctioning ileostomy.

(D) Following the subsidence of Crohn's disease *diverticula appeared* in an area of bowel previously affected by Crohn's disease—two cases. It is not known whether symptomless diverticulosis had been present in these two cases before the development of Crohn's disease.

CASE HISTORIES

Case 1

This 61-year-old housewife gave a six month history of worsening diarrhoea, latterly with blood in the stools, and two stone weight loss. Examination revealed a thin, pale, anxious woman. Anal skin tags were present. Haemoglobin 9 g.%. Sigmoidoscopy, under anaesthesia, showed reddening and irregular granularity of the rectal mucosa. Histology of rectal biopsies showed non-specific inflammatory changes.

Barium enema (27.2.59) showed narrowing and deep ulcers in the upper descending colon and the distal transverse colon. On the pelvic and iliac colon there were multiple diverticula (Fig. 1, a and b). Treatment with intramuscular corticotrophin gel was followed by considerable symptomatic improvement, but the patient returned five months later with a relapse. At this time sigmoidoscopy showed similar changes but histology on this occasion revealed the presence of granulomata. Cortico-steroids resulted in a remission but relapse occurred after three months.

A barium enema at this time (18.3.60) showed extension of the disease proximally to the mid-transverse colon, where there were undermined ulcers, and distally to the iliac and pelvic colon where typical hyphen ulcers (Berridge, 1975) were seen. The descending colon was devoid of haustration. The affected part of the colon and rectum were narrowed and the post-rectal space increased. The diverticula, which had been present on the pelvic and iliac colon, had disappeared (Fig. 2, a and b).

Progress was less satisfactory on further treatment with cortisone, and colectomy and ileostomy were performed four months later. The resected specimen showed Crohn's disease involving the caecum and the whole of the remainder of the colon, apart from the lowermost 10 cm of the ascending colon. No diverticula were present in the specimen.

Case 2

A 49-year-old housewife presented with four months history of constipation with blood and slime in the stools. A diffusely reddened and oedematous mucosa was seen on sigmoidoscopy. Barium enema (5.1.65) showed diverticula on the distal transverse colon, descending colon and pelvic colon, but no other abnormality (Fig. 3). Treatment with sulphasalazine and courses of prednisolone retention enemata was followed by some improvement. Two years

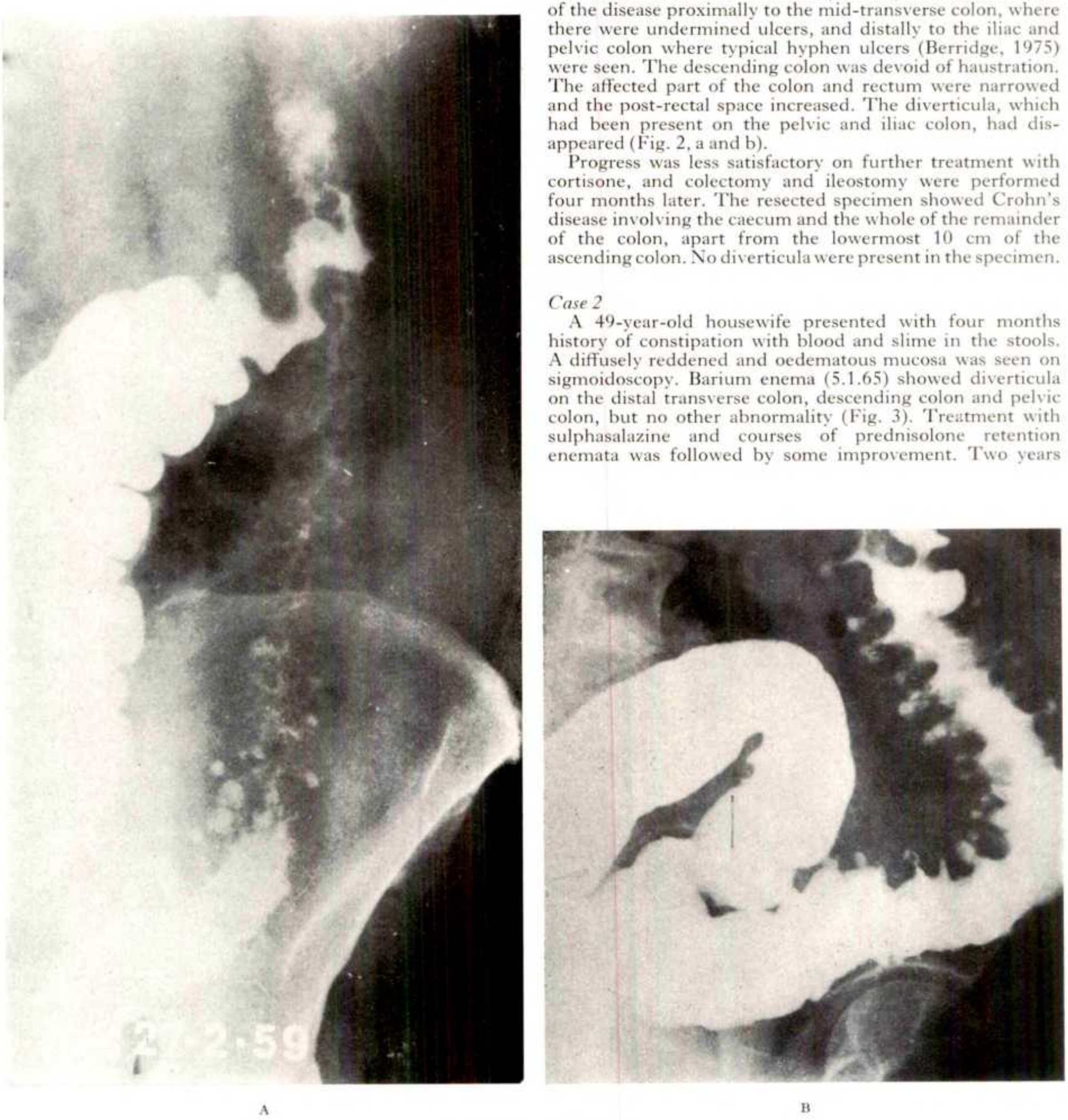

FIG. 1. *Case 1.* 27.2.59.

(A) Narrowing of the distal transverse colon. Diverticula on the descending and iliac parts of the colon.

(B) Diverticula on the pelvic colon.

after the onset she developed an arthritis in several finger joints and a painful sacro-iliitis. At that time, barium enema (15.2.67) showed a few diverticula on the pelvic colon only and some narrowing of the rectum (Fig. 4).

The joint symptoms subsided on treatment but shortly after this the picture changed with the development of diarrhoea, anal skin tags and an irregular cobblestone appearance in the inflamed rectum. Rectal biopsy showed non-specific inflammatory changes. Local steroid therapy produced some improvement but 18 months later she developed worsening diarrhoea and progressive anaemia, requiring transfusion. Barium enema (18.11.68) showed narrowing of the rectum and a cobblestone mucosal pattern

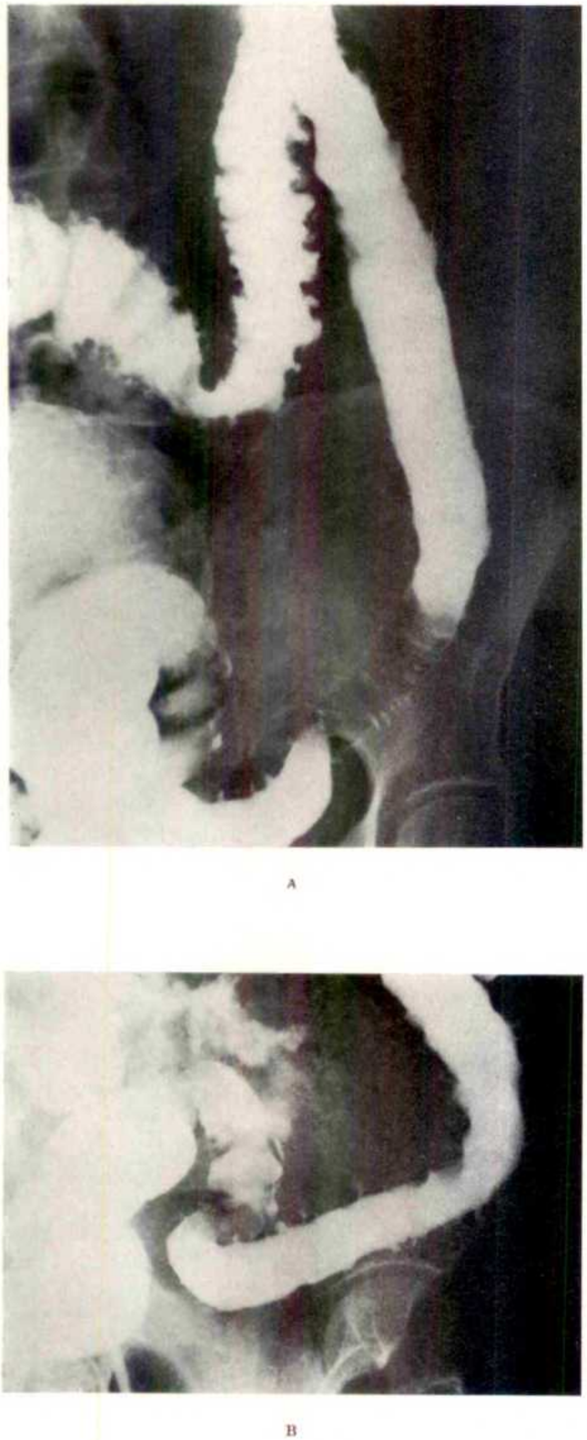

FIG. 2. *Case 1.* 18.3.60.

(A) The diverticula on the descending and iliac colon no longer seen. Hyphen ulcers on the iliac colon.

(B) Deep ulcers on the pelvic colon.

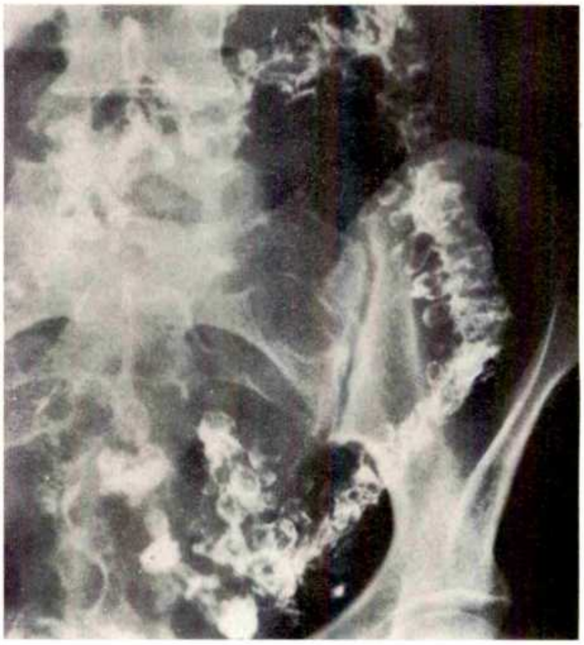

FIG. 3. *Case 2.* 5.1.65.

Diverticula on the whole of the left side of the colon.

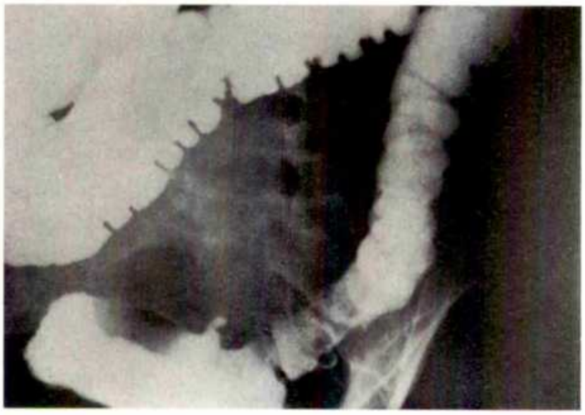

FIG. 4. *Case 2.* 13.2.67.

Fewer diverticula now seen and only on the pelvic colon.

in the pelvic colon with a few deep ulcers. The diverticula in the pelvic colon had completely disappeared (Fig. 5). Shortly after this examination the patient became distended and laparotomy was performed. The pelvic colon was diffusely indurated and oedematous and the whole colon distended. An ileostomy was carried out.

Following this her general condition improved considerably. Barium enema (9.1.69) carried out on the defunctioned colon showed a return of the diverticula in the pelvic colon and the cobblestone appearance of the mucosa could no longer be demonstrated (Fig. 6). Procto-colectomy was subsequently performed on 13.1.69, 8 cm of ileum also being removed. The wall of the ileum showed typical changes of Crohn's disease while throughout the colon there were scattered areas of mucosal ulceration and pseudopolyp formation, with extensive ulceration in the anal region.

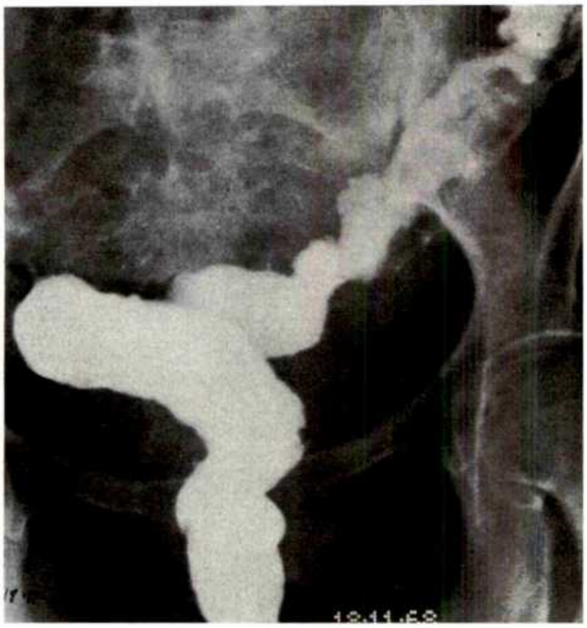

FIG. 5. *Case 2.* 18.11.68.
Cobblestone appearance in the pelvic colon with a few deep ulcers.

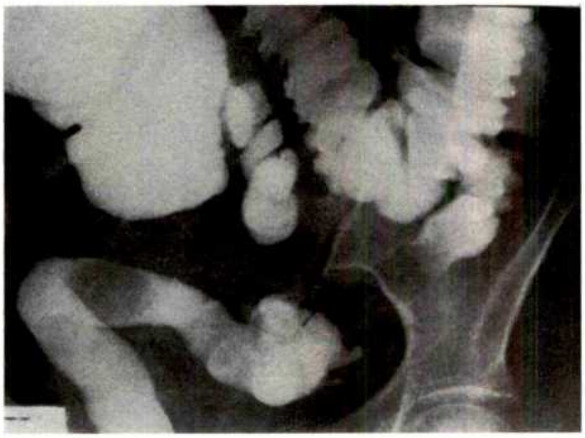

FIG. 6. *Case 2.* 9.1.69.
The diverticula have re-appeared on the pelvic colon. The cobblestone mucosal pattern is no longer seen.

DISCUSSION

The association of diverticular disease and Crohn's disease in the same segment of colon is of considerable interest. Although the establishment of the diagnosis of diverticular disease in a length of colon obviously affected by Crohn's disease, and vice versa, may be extremely difficult radiologically, it is usually possible. This allows an assessment to be made of the changes which occur in the colon over a period of time.

The disappearance of diverticula with the development of Crohn's disease and their reappearance in remission is probably related to the tone of the bowel wall, which in turn is affected by the amount of induration and oedema and/or fibrosis present. It is generally accepted that diverticular disease is caused by increased intraluminal pressure and certainly diverticula are more numerous radiologically when the colon is contracted than when it is relaxed. Inflammatory disease of the bowel radiologically appears usually to be associated with incomplete contraction and diminution or absence of stripping waves. This is seen not only in Crohn's disease, but also in ulcerative colitis, and in both these conditions the loss of function of the bowel may prevent the demonstration of the radiological post-evacuation surface pattern. The combination of diverticula with ulcerative colitis is much rarer than with Crohn's disease, no doubt due to the fact that ulcerative colitis tends to occur in a younger age-group than does diverticular disease.

It cannot, of course, be concluded that the presence of inflammation in the bowel wall inhibits the formation of diverticula, but it does appear from these cases that inflammation due to Crohn's disease may result in the disappearance of diverticula, and that they may sometimes appear after subsidence of the inflammatory process. These points may be relevant to the interpretation of barium enema findings in these conditions.

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Giant gas filled cysts of the sigmoid colon: a report of two cases

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ABSTRACT

Two case reports of giant gas filled cysts of the sigmoid colon are presented. It is considered that radiology provides the only useful and conclusive diagnostic investigation. In one of the cases, operative confirmation was obtained. In the other, the radiological appearances are considered to be diagnostic.

Less than 30 single case reports have been recorded of giant gas filled cysts of the sigmoid colon. They are considered to be a rare complication of diverticular disease of the sigmoid colon, and to represent a giant sigmoid diverticulum. Comprehensive reviews have been made by Sibson and Edwards (1972) and Moss (1975). We report two further cases which illustrate the important features.

CASE HISTORIES

Case 1

A 78-year-old woman presented with angina of effort, some nausea and vomiting for the previous two weeks, and occasional pains in the centre of the abdomen for one year.

A plain film of the abdomen showed a large gas filled cystic lesion in the right lower abdomen (Fig. 1). The barium meal examination showed no abnormality. A follow through examination showed no abnormality in the small bowel but, in the film taken at 24 hours (Fig. 2) barium was demonstrated within the cystic cavity which communicated with the pelvic colon. On following Out Patient visits the patient had no abdominal symptoms. Abdominal examination ten months after her first visit revealed a soft, round mobile mass in the right abdomen. A plain film at that time showed that the diameter of the cyst had altered from 13 to 15 cm, an increase in cyst volume of 50%. No change in the diameter of the cyst was seen on supine views, which were taken in the straining and non-straining states.

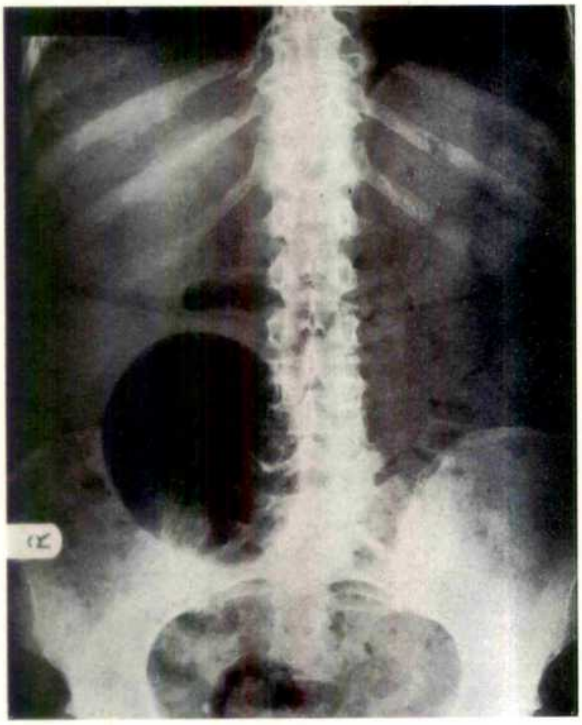

FIG. 1.

Large gas filled cyst in lower abdomen.

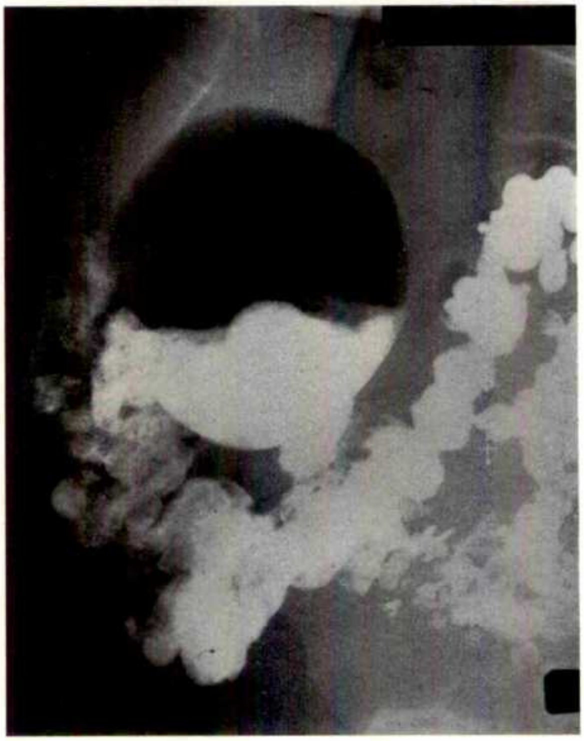

FIG. 2.

At 24 hours, barium has passed from the sigmoid colon into the cyst. Diverticular disease is shown.

Case 2

A 67-year-old man presented with relative constipation and intermittent lower abdominal pains of a few weeks duration. An immobile non-tender mass was present in the right iliac fossa. A provisional diagnosis of carcinoma of the caecum was made. Four days later clinical examination revealed a threefold increase in size of the mass. At this time, an abdominal film showed a translucent cystic structure 13 cm in diameter containing a fluid level. Barium enema disclosed diverticular disease of the sigmoid colon and lower descending colon. No barium entered the cystic structure which was related to the sigmoid colon. The following day he was admitted complaining of pain in the right iliac fossa. Findings included temperature of 37.5°C and W.B.C. 13000. Laparotomy was indicated. The sigmoid colon with attached cyst was removed, the distal colon brought to the skin and the stump closed (Hartmann's procedure).

Pathological report

Sections confirmed many diverticula with active chronic diverticulitis. The wall of the cyst which was about 3 mm thick, consisted of fibrous tissue, covered on its inner lining by fibrino-purulent exudate. There was no enterogenous tissue in the cyst wall. Macroscopic examination revealed a cystic structure 10 × 6 cm attached to the serosal surface of the large intestine. The 3 mm thick cyst wall, comprised of white fibrous tissue was thinned opposite to its attachment to the intestine. No definite connection between this cyst and the intestine was found, but several diverticula were present in the colonic wall adjacent to the cyst.

DISCUSSION

Giant gas filled cysts of the sigmoid colon occur in middle and old-age groups with equal distribution between the sexes. They vary in diameter from 10 to 30 cm and arise from the anti-mesenteric border of the sigmoid colon. The cyst wall is composed of fibrous and granulation tissue and varies in thickness from 3 to 10 mm.

Plain, supine, erect and lateral decubitus views of the abdomen show large air-filled cystic structures situated in the middle and lower abdomen, commonly with a fluid level. Barium enema examination with one reported exception (Vanapruks and Fuhrman, 1969), demonstrated diverticular disease of the sigmoid colon related to the cystic structure. In the 30 reported cases which include our two examples, 12 cases have shown fluid levels and eight cases have shown a communication on barium studies. Case 1, who is the oldest recorded patient with a giant sigmoid diverticulum, is the first patient in which the associated diverticulur disease has been shown on follow-through examination. Clinical presentation varies widely, ranging from acute symptoms with abdominal pains (Case 2) to relatively asymptomatic cases (Case 1). The only complications reported are one case of perforation (Macbeth and Riddle, 1964), and one of volvulus (Silberman and Thorner, 1961). Surgical treatment has been advised and performed. It is of interest that no surgical treatment has been performed in Case 1 and the patient remains asymptomatic during the ten months following the initial diagnosis.

There are few conditions which need to be considered in the differential diagnosis. Enteric cysts usually occur in younger patients, are oval in shape, related to the mesenteric border, are smaller in size, contain smooth muscle in their wall and rarely show communication with the gut. Giant duodenal diverticula, emphysematous cholecystitis and the rare cystic dilatation of Meckel's diverticulum may be excluded by their relation to the small bowel. Pelvic abscesses, which may contain a small amount of air, and volvulus of the large bowel can be excluded by their radiological and clinical features.

ACKNOWLEDGMENTS

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Stenosis of the deep femoral artery: an evaluation of the accuracy of single-plane, anteroposterior arteriograms

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ABSTRACT

Pre-operative evaluation of the deep femoral artery is important in determining surgical treatment of aorto-femoral disease. We reviewed 16 years' experience in bilateral aorto-femoral by-pass grafting and found that 63.2% of stenoses of the deep femoral arteries seen at surgery had been missed on conventional antero-posterior arteriograms. These findings demonstrate the inadequacy of a single, antero-posterior projection and the need for supplementary views in assessing lesions of the deep femoral artery.

In ischaemic disease of the lower extremity, the deep femoral artery is often the major source of limb survival. Its involvement with atherosclerosis is usually less extensive than is the superficial femoral artery's, and in many cases the deep femoral artery becomes the only supplier of blood to the leg (Beales *et al.*, 1971).

Recent and improved surgical reconstructive techniques rely heavily on pre-operative detection and diagnosis of lesions of the deep femoral artery. It is standard practice in most hospitals to perform single-plane, antero-posterior (AP) arteriography of the femoral vessels to assess ischaemic disease. We investigated the adequacy of traditional, single-plane, AP arteriography by comparing the arteriographic results with those found at reconstructive surgery.

MATERIALS AND METHODS

Over a 16-year period (May 1959 through August 1975), 195 patients at our institution underwent bilateral aorto-femoral by-pass grafting (390 femoral anastomoses). In each instance the distal graft anastomosis was made to the common femoral artery, and under direct vision the origins of the superficial and deep femoral arteries were examined.

Each patient had previously undergone single-plane, AP arteriography by translumbar approach (1959 to 1971) or by percutaneous catheterization (1971 and thereafter). Radiographs and operative reports were reviewed for each patient.

RESULTS

At surgery, the origin of the deep femoral artery was found to be stenotic in 76 instances and occluded in four. Pre-operative arteriography had predicted only 28 stenoses—a false-negative rate of 48/76 or 63.2%.

DISCUSSION

Pre-operative detection of stenosis of the deep femoral artery is important for two reasons. First, stenosis of the deep femoral artery significantly affects surgical prognosis. Malone *et al.* (1975), retrospectively analysed the results of 15 years of aorto-femoral by-pass grafting. They found the graft limb patency rate at five years after operation to be 96% in patients who had no popliteal trifurcation disease, 75% in patients having stenosis or occlusion of the proximal deep femoral artery, and 0% in patients who had lesions of both the deep femoral artery and the popliteal trifurcation (Table I). Second, awareness of the presence of stenosis will change the operative approach. Malone *et al.* (1975) determined that prophylactic angioplasty of the affected deep femoral artery can result in markedly improved (graft) patency rate. They recommend that "even when stenosis does not appear to be substantial at surgery all profunda femoris artery lesions should be reconstructed". The above statistics clearly point out how, in a poor-risk patient with trifurcation disease, knowledge of the presence of deep femoral artery lesions is critical in determining surgical therapy.

TABLE I

GRAFT LIMB PATENCY, FIVE YEARS AFTER OPERATION*

Vascular lesions	Patent grafts, %
No distal disease	96
Profunda femoris stenosis or occlusion only	75
Popliteal trifurcation disease only	66
Tandem lesions (profunda femoris and tibial trifurcation)	0

*After Malone, Moore, and Goldstone (1975).

The inadequacy of the AP projection in evaluating lesions of the deep femoral artery derives from the postero-lateral origin of this vessel at the common femoral artery. The proximal segment of the deep femoral artery is foreshortened and often overlaps the superficial femoral artery on the frontal projection. Moreover, a single-plane arteriogram of any vessel gives only a two-dimensional view of its lumen. Moore and Hall (1971) have shown that a high-grade stenosis in the anterior or posterior portion of a vessel can be obscured by a flat lumen filled with contrast material.

Thomas and Andress (1972) reported that 30 deg. anterior oblique projections demonstrate the origin of the deep femoral artery in 90% of instances, as opposed to 40% using the frontal view. The results of our study strongly suggest that in the evaluation of ischaemic disease of the peripheral vasculature, the AP projection is inadequate and should be supplemented by additional views.

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Book review

Fundamentals of Radiology. By Lucy Frank Squire, pp. xv + 366, 1975 (Commonwealth Fund Book, Harvard University Press, Cambridge, Mass., and London), £11·60.

This is a revised edition of the same author's *Fundamentals of Roentgenology*. I met the book after completing my first year in radiology, and had been told then that it was "much too elementary". I quickly found out what a sad and stupid misappraisal that was. I hope no radiology trainee has ever been put off Dr. Squire's book just because it is ostensibly addressed to medical students, aiming to give them a basic outline of how radiology works. Any medical student who masters the volume is well on the road to becoming a radiologist.

The new edition has revisions in the text and illustrations. Dr. Squire is a marvellous teacher who captures the reader's interest irresistibly. There are the expected question-and-answer games, the challenging puzzles that are only solved as the next few pages are digested. She moves from the elementary bricks of X-ray findings on chest, heart and abdomen films to build the simple, common diagnoses we meet every day. There are also sections on bone and on contrast medium studies. All this is done on a solid base of understanding these bricks and the way they are put together: the book will not make you a master builder overnight, but will give any apprentice a head start to last a lifetime.

Training departments that still do not have the earlier book had better buy this new edition quickly: it is a bargain at the present price. The many illustrations and radiographs, often comparing pathology specimen and X-ray film, are clear and beautiful. Their careful setting out on each page is an object lesson. Much care and talent has gone into this work.

I am surprised by one part of Dr. Squire's message. There are repeated reminders in the text that the business of diagnosis from radiographs is systematic information-gathering-by-rote. This is the traditional base of medical teaching, in conflict with the newer understanding that science is essentially a questing, trial-and-error, problem solving activity. It seems to me that Dr. Squire's book is itself a brilliant teaching exercise in problem solving, so that the message about the primacy of collecting data appears rather tired and out of place. This is more than a philosophic quibble. We have a challenging crisis on our hands to make medicine care- and cost-effective. In the diagnostic disciplines we will have to move away from the awful establishment ideal of the diagnostic work-up ("find out everything first, then see what's wrong") to the notion that the most simple, selective, elegant diagnostic pathways are best ("what's wrong?"). In teaching this is a question of emphasis, and in the event Dr. Squire's book strikes me as a marvellous example of how to get everything right. Read it.

T. SHERWOOD.

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The radiology of sclerosteosis

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Abstract

Sclerosteosis is an unusual disorder in which increased skeletal density is associated with abnormalities of bony modelling. The condition is progressive and complications arise due to cranial nerve involvement. Death from raised intracranial pressure occurs in early adulthood.

In order to define the range and extent of the bony abnormalities, the radiographic features of 18 affected individuals have been analysed. The recognition of characteristic changes permits diagnostic precision.

Increased skeletal density and abnormalities of bony modelling are features of a number of uncommon genetic disorders. These conditions have often been grouped together as "osteopetrosis", "Albers-Schönberg disease", or "marble bones". However, in recent years a number of entities with consistent and characteristic clinical and radiographic stigmata have been separated from this general category.

Sclerosteosis is a disorder of this type which has attained the status of a distinct entity. In order to define the radiographic features of this condition, which is virtually confined to the Afrikaner population of Southern Africa (Beighton *et al.*, 1976) we have studied 18 affected individuals. The radiographic findings are presented and discussed in this paper.

Classification

Understanding of the "osteopetrosis" group of disorders has been greatly facilitated by the classification proposed by Gorlin *et al.* (1969), following their critical review of the literature concerning these conditions.

1. *Osteosclerosis*

In these conditions increased radiological density of bone is the predominant feature. Abnormalities of bony modelling, if present, are of minor degree. The autosomal dominant and autosomal recessive forms of true osteopetrosis, together with pycnodysostosis, are the most important disorders in this group.

2. *Craniotubular dysplasias*

Abnormal modelling of the skeleton is the major feature of this group of disorders, while increased radiological bony density is of lesser degree. Involvement of the cranium may lead to nerve compression and complications include facial palsy and deafness. Pyle's disease, the autosomal dominant and recessive types of craniometaphyseal dysplasia, and rarities such as craniodiaphyseal dysplasia and frontometaphyseal dysplasia fall into this category.

3. *Craniotubular hyperostoses*

Overgrowth of the cranium and tubular bones predominate, while increased radiological density is less marked. Sclerosteosis, the subject of this presentation, features in this group together with van Buchem's disease, osteoectasia and Engelmann's disease.

4. *Miscellaneous*

Disorders which do not fall into any of the three previous categories, but which have sometimes been considered as forms of osteopetrosis include melorrheostosis, osteopoikilosis and osteopathia striatum.

Patients Studied

During the course of a nation-wide survey of skeletal dysplasias in South Africa, 21 patients with sclerosteosis were examined. These individuals, who were members of 15 separate kindreds, were all of Afrikaner stock. The pattern of transmission of the condition in these families was consistent with autosomal recessive inheritance.

Radiographic studies were undertaken in 18 of these patients, nine males and nine females, their ages ranging from nine months to 56 years. The description of their radiographic features forms the subject of this paper.

Clinical Features

Individuals with sclerosteosis are unusually tall, adult males generally exceeding 198 cms. in height, while females may attain 183 cms.

Overgrowth of the cranium leads to distortion of the facies, the brow and lower jaw becoming massive. Facial palsies consequent upon cranial nerve compression contribute to the abnormal appearance and the affected individual's problems are compounded by the development of deafness and involvement of the optic nerve (Fig. 1). Death in early adulthood is the usual consequence of progressive rise in intracranial pressure (Beighton *et al.*, 1976).

Syndactyly of the 2nd and 3rd fingers is a prominent feature. This abnormality is variable in degree, ranging from cutaneous webbing to complete bony fusion (Fig. 2). The digits are mis-shapen, with radial deviation of the terminal phalanges, and the nails may be dysplastic.

RADIOLOGICAL FEATURES

The outstanding radiographic changes in the affected individuals were massive increase in the size and density of certain components of the skeleton, the skull and tubular bones being predominantly involved.

The manifestations were age-related. The skull radiographs of three unequivocally affected children aged nine months, three and a half and five years were ostensibly normal, and their hand radiographs revealed no bony changes other than syndactyly. However, definite thickening of the skull and distortion of the phalanges were present in a seven-year-old girl. All the children examined had a normal epiphyseal age development.

In older individuals the bony density and abnormal modelling became increasingly evident throughout childhood and early adult life before apparently becoming static by the end of the third decade.

Skull

The major feature was a dense thickening of the calvarium with complete obliteration of the diploic space (Fig. 3). The increase in bone density and width commenced from the inner table of the cranial vault and progressed so that the internal diameter of the cranium was reduced by adulthood. The frontal sinuses were enlarged, the vascular markings were prominent and the occipital venous sinuses were often well outlined. The bones of the base of the skull were particularly dense and narrowing of the exit foramina was confirmed by tomography in three patients. The sella turcica was enlarged and rounded in six of the 12 adults.

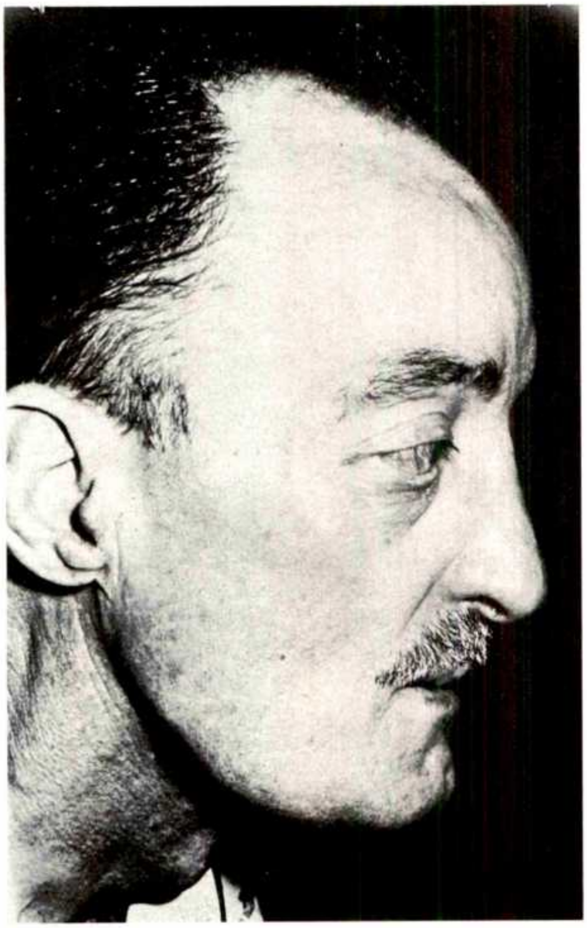

FIG. 1.

The characteristic facies in sclerosteosis–a 45-year old male with mandibular hyperplasia, facial palsy and proptosis.

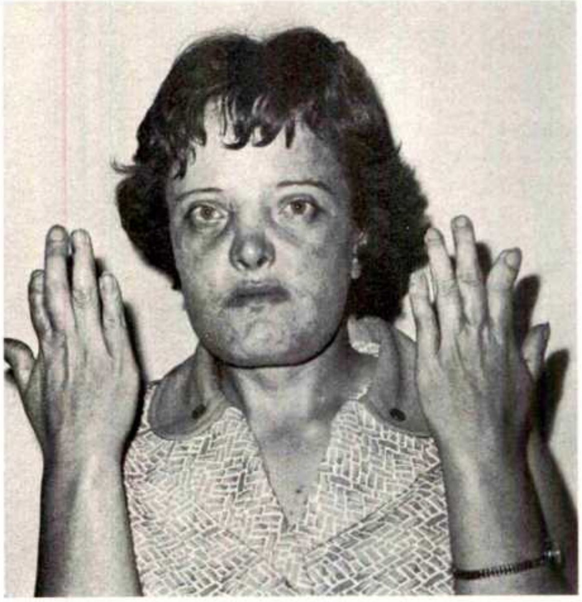

FIG. 2.

Sclerosteosis in a 33-year-old female. Soft tissue syndactyly of the 2nd and 3rd fingers has been surgically corrected.

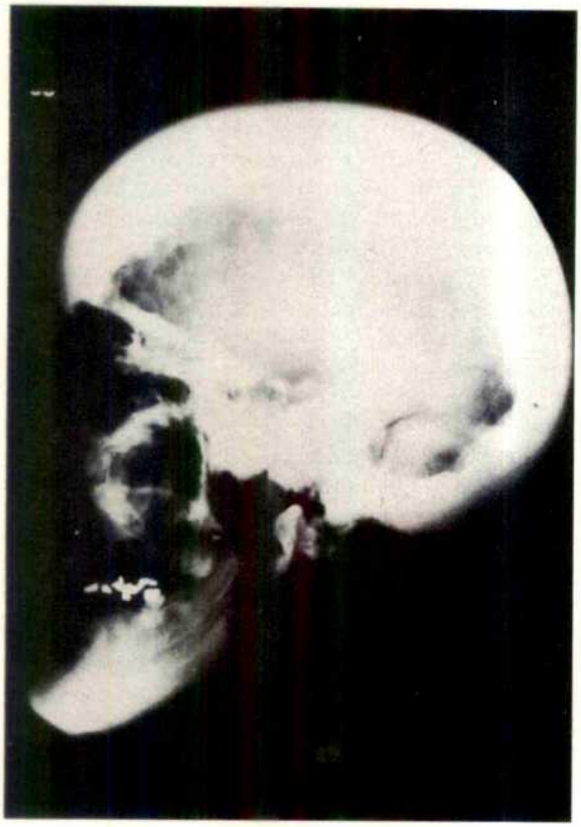

FIG. 3.

Skull radiograph, lateral. Increased density and width of the calvarium is a major feature. The mandible is massively enlarged.

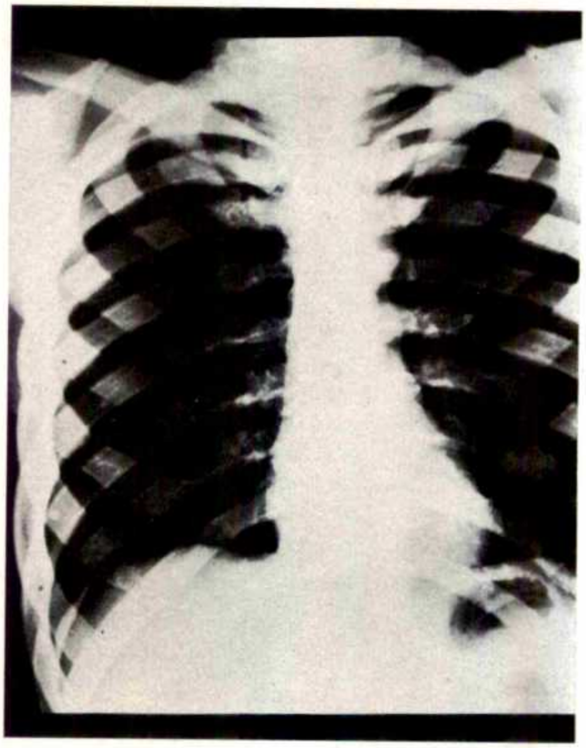

FIG. 4.

Chest radiograph. The clavicles and ribs are widened and dense.

The body of the mandible was massively enlarged in the adults, with resultant prognathism. The jaws were usually edentulous or deficient in teeth and the density of the bone was such that it was not possible to recognise the lamina dura.

Thorax

The clavicles were generally enlarged, the thickening and widening being most marked medially. The ribs were widened with increased density so that the inner texture of the bones was not readily visible (Fig. 4).

Vertebrae

Changes in the vertebrae were confined to their posterior aspects, notably the pedicles and laminae of the lumbar and sacral vertebrae (Fig. 5). The vertebral bodies showed no increase in density. The only degenerative changes noted in the intervertebral disc spaces were present in a 35-year-old male.

Pelvis

Increase in density predominantly involved the lower portions of the iliac bones and the ischial and pubic rami. Bony outlines were generally normal although relative hypoplasia of the iliac wings was a consistent feature (Fig. 6.).

Tubular Bones

These bones were massive, with marked cortical thickening and some degree of disturbance of modelling (Fig. 7). The thickening of the cortex generally extended along the whole length of the shafts. However, in the femora the cortical thickening was confined to the upper two thirds, while the lower third had an abnormal configuration, the metaphyseal region being widened, with lack of normal diaphyseal constriction (Fig. 8).

The hand changes were an outstanding feature of the condition (Figs. 9 and 10). Every patient had some degree of syndactyly and the tubular bones of the hands were enlarged, dense and distorted with radial deviation of the terminal phalanges. In the only patient in whom the feet were X-rayed, the metatarsals and phalanges showed similar features.

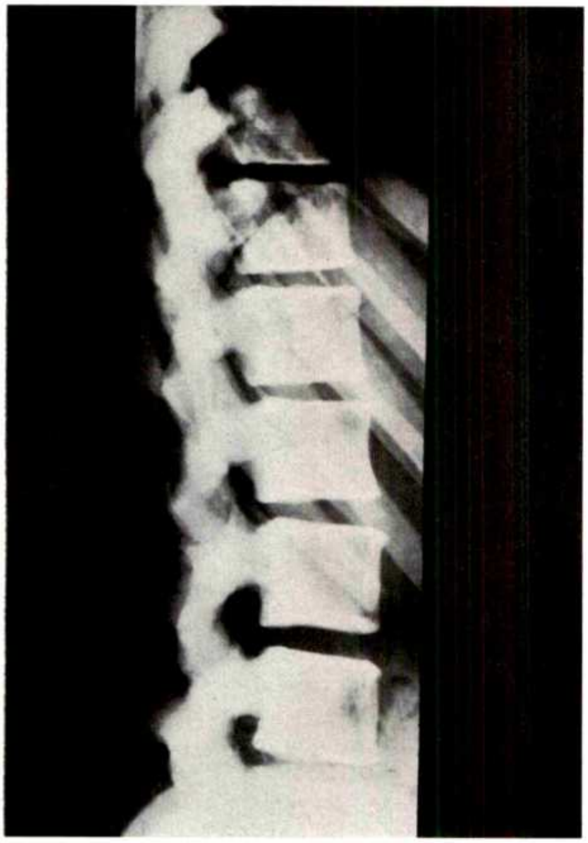

FIG. 5.

Lumbar spine—lateral radiograph. The vertebral bodies are relatively normal, increased bony density being of significant degree only in the pedicles.

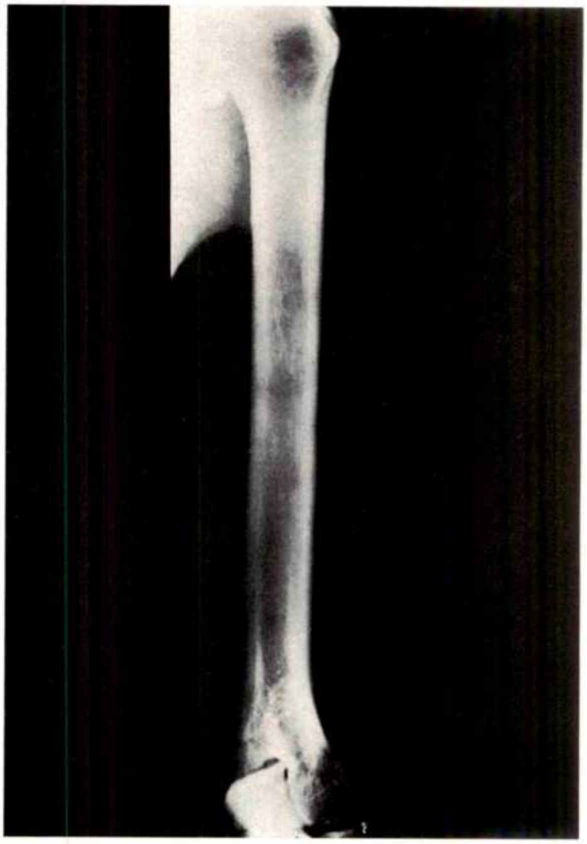

FIG. 7.

Humerus—antero-posterior radiograph. The cortex is thickened and bony modelling is disturbed.

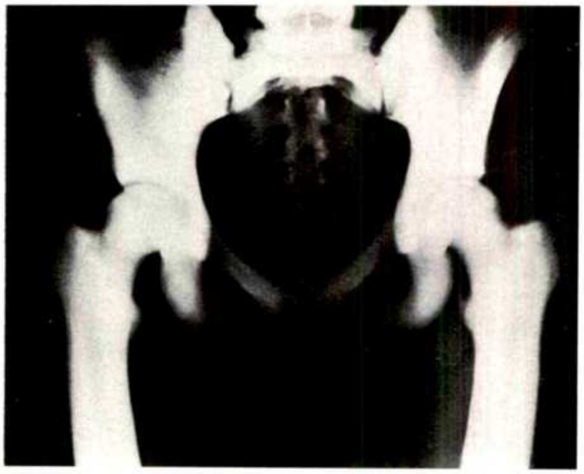

FIG. 6.

Pelvis—antero-posterior radiograph. Density is increased particularly in the lower portions of the iliac bones and in the ischial and pubic rami. The iliac wings are relatively hypoplastic.

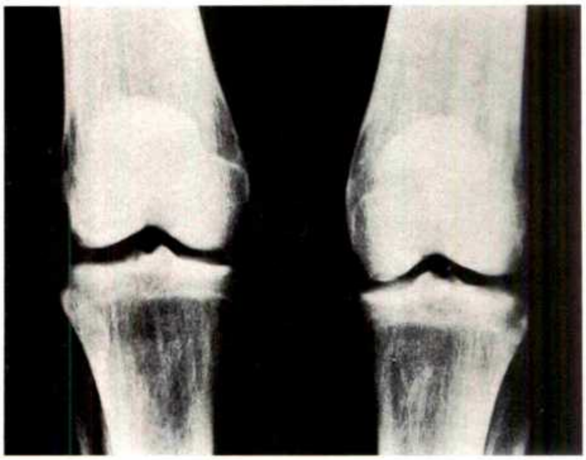

FIG. 8.

Knees—antero-posterior radiograph. Modelling defects are particularly evident in the lower ends of the femora, where the metaphyseal region is widened.

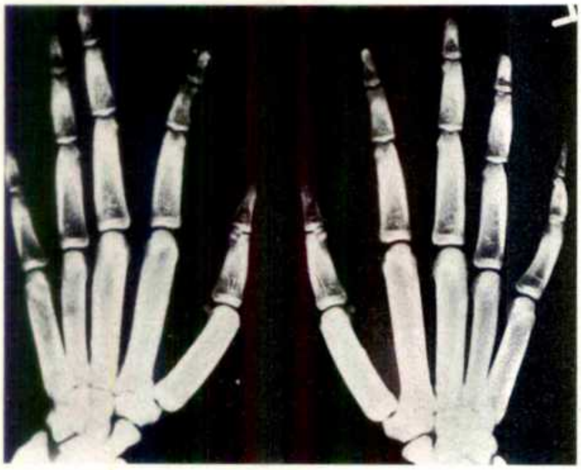

FIG. 9.

Hands—antero-posterior radiograph. Changes in the bones of the hands are a prominent feature of sclerosteosis. The shafts of the metacarpals and phalanges are distorted, with increased cortical thickening.

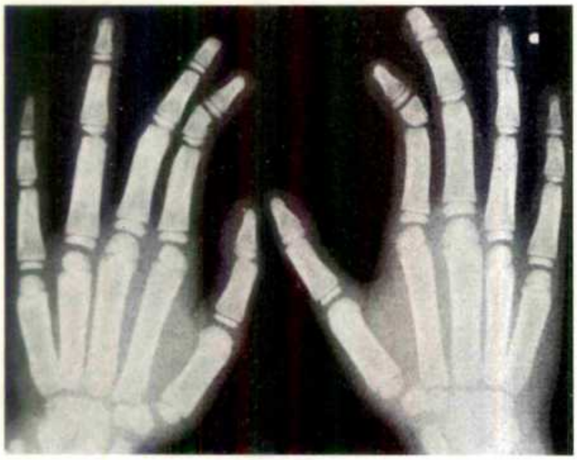

FIG. 10.

Hand—anterior-posterior radiograph. Syndactyly of the 2nd and 3rd fingers is variable in degree. This patient has marked soft tissue union and phalangeal malformation.

DISCUSSION

Although sclerosteosis is a rarity, there is no doubt that it is a separate and distinct entity. In the past, a few case reports appeared under the loose designation "osteopetrosis". Truswell (1958) first recognized that the condition was a unique disorder, to which Hansen (1967) later applied the designation "sclerosteose". Although by no means a true description of this condition, the appellation of "sclerosteosis" has now gained popular acceptance. Other than the Afrikaner patients, the only other case reports have concerned a kindred in New York (Kelley and Lawlah, 1946) and a girl in Japan (Sigiura, 1975).

Sclerosteosis is a potentially lethal disorder, and early death is preceded by distressing complications. For this reason, diagnostic precision is of paramount importance, as this will permit accurate prognostication and rational genetic counselling. At the present time therapy is limited to surgical decompression of entrapped cranial nerves, craniotomy to relieve raised intracranial pressure, cosmetic surgery to the face and hands, and the provision of a hearing aid.

The radiological features of sclerosteosis bear some resemblance to those of virtually all the disorders mentioned in the classification section. However, the syndactyly and severe distortion of the phalanges serves to distinguish sclerosteosis from these conditions. Furthermore, sclerosteosis is the only disorder in this group in which excessive height occurs. The facial changes and tall stature gives sclerosteosis a superficial resemblance to acromegaly. Nevertheless, even in patients with enlargement of the sella, radiographic distinction is an easy matter, as cranial hyperostosis and modelling defects of the long bones are not features of acromegaly. In this context, it may be relevant that extensive investigations in two of our patients with sclerosteosis have revealed no endocrine abnormality.

In our experience, the only condition which could be confused with sclerosteosis is van Buchem's disease (hyperostosis corticalis generalisata). One of the authors (H.H.) visited Holland to examine affected individuals and concluded that the disorders differ in that patients with van Buchem's disease are of normal stature, have less distortion of the face and have little involvement of the hands. This contention is supported by the case descriptions of eight patients published by van Buchem (1971), none of the individuals having syndactyly or other significant digital involvement.

As sclerosteosis is transmitted as an autosomal recessive, an affected individual must inherit an abnormal gene from each of his parents in order to develop the disorder. These "carrier" parents are themselves clinically normal. On a basis of the prevalence of sclerosteosis in South Africa, it can be calculated that at least one in 140 individuals of Afrikaner stock is a heterozygote or carrier of the gene.

This population prevalence is of practical significance for the radiologist, as it is possible that the carrier might be detected by the recognition of minor degrees of widening and loss of trabeculation of the calvarium (Beighton and Hamersma, 1974). This problem is presently under investigation, as a reliable technique for determination of carrier status would have far reaching implications for eventual control of the disorder.

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Book review

The upper brain stem in the human: its nuclear configuration and vascular supply. By B. Schlesinger, pp. 266, illustrated, 1976 (West Germany, Springer-Verlag) $159.90.

This book describes the anatomy of the upper brain stem in great detail. It is based on painstaking anatomical dissections performed by the author and on his study of collections of myelin stained specimens.

The author first describes in considerable detail his method of making and analysing oblique sections of the brain stem in a way which allows him to reconstitute a three dimensional matrix which depicts the precise spacial relationships of the structures in the sections. In this way he has established the form, position and variation of nuclei, fibretracts and of the fine vascularization. In 36 specimens the vessels were injected in various ways and then studied by radiography and by anatomical sectioning. There is an excellent discussion on the variations in vascular anatomy, which confirms that the usually described pattern is an idealized conception and that the exception to this pattern is the rule. Finally, there is a short chapter on the syndromes associated with specific vessel occlusions.

Unfortunately, some of the nomenclature varies from that generally accepted by neuroradiologists, although the latter is usually referred to in discussion. The book is beautifully illustrated with photographs of dissections, radiographs of specimens and excellent diagrams. A great deal of the minute anatomy is of much greater interest to neurosurgeons and neuroanatomists than to neuroradiologists, but the chapters on variation of the larger vessels are of neuroradiological interest and will be useful for reference.

B. E. KENDALL.

1976, *British Journal of Radiology*, *49*, 940–943

Placental localization: a comparison of isotopic and ultrasonic placentography

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ABSTRACT

Two-hundred-and-ninety patients were investigated using both isotopic and ultrasonic methods in order to determine accurate placental localization: results are compared.

Accurate placental localization is important in investigating antepartum haemorrhage because accurate diagnosis of placenta praevia has an important influence on the management of the patient. Conversely, unnecessary stay in hospital can be avoided by excluding placenta praevia (Donald and Abdulla, 1968).

The most accurate radiological method of placentography is arterial placentography (Sutton, 1974) but in most centres it has been superseded by isotopic placentography because this is thought to be a reliable method which is less exacting for the patient, and which has a smaller radiation hazard (Wright, 1970; Aiers *et al.*, 1969). Ultrasonic placentography is now being used with increasing frequency because it is completely non-invasive and is radiation free (Donald and Abdulla, 1968; Hellman *et al.*, 1970; Abdulla *et al.*, 1972). Many consider that it is the method of choice (Kukard and Freeman, 1973) whereas others have not found ultrasonic methods serious competitors to isotopic methods (Cryer *et al.*, 1970).

In order to try to resolve these differences in opinion, the results of isotopic and ultrasonic placentography in 290 patients have been analysed in detail.

PATIENTS

Two-hundred-and-ninety patients were investigated between 26 and 40 weeks gestation because of suspected placenta praevia.

Two-hundred-and-thirty-two of these presented with an antepartum haemorrhage and 58 with a high presenting part or unstable lie of the fetus.

All patients had isotopic placentography, 265 using a gamma-camera and in the remaining 25 a rectilinear scanner was used.

One-hundred-and-seventy-five patients had ultrasonic placentography as well as isotopic placentography.

METHODS

Isotopic

250–500 μCi ^{113}In^{m} chloride were used in all isotopic scans. After intravenous injection ^{113}In^{m} is bound to transferrin which does not cross the placenta to any degree (Johnson *et al.*, 1969). A small amount of activity is excreted in the urine and this is greater when the transferrin is fully saturated (*e.g.* after intravenous administration of iron). Therefore, the images were done immediately after injection and the rectilinear scans were started at the level of the symphysis pubis to avoid interference from radioactivity in the bladder (Wright, 1970). The appropriate lateral projection was then done. Markers were placed on the scan corresponding to the anterior superior iliac spine and the symphysis. A similar technique was used with the gamma-camera.

The chemical dose of Indium is negligible. The maternal and fetal radiation doses are as low as 5 and 4 mrad/500 μCi respectively, roughly equal to one week's naturally occurring background radiation (Wright, 1970).

Ultrasonic

Ultrasonic scans were done with an apparatus constructed by the Department of Medical Physics at Bristol General Hospital. This is an apparatus with a jointed arm carrying the transducer over the patient couch. The couch can be rotated about its centre, allowing change from longitudinal to transverse scan planes without moving the patient. The gantry holding the arm may be moved laterally to produce measured parallel scan planes.

The apparatus operated at 2 MHz and has three display cathode-ray tubes. Two of them are used to display the section scan, one being a long persistence tube viewed by the operator, and the other is used to provide a photographic record on Polaroid film. The third display tube shows the A-scan and swept-gain functions. Most of the patients had a full bladder at the time of operation. The lower segment of the uterus is taken as that area within 5 cm of the internal os.

TABLE I

DIAGNOSTIC ACCURACY OF ISOTOPIC AND ULTRASONIC SCANS

Scan	Patients with placenta praevia	Patients without placenta praevia	Scan positive	False negative	False positive
Isotope	44	246	33	11	5
Ultrasound	29	146	27	2	10

RESULTS

The placental site was shown in 24 out of 25 patients examined by rectilinear isotope scanning. The placental site was not demonstrated in two of the 265 patients examined by gamma-camera and its location was doubtful in a further two cases. None of these patients in whom placental localization was not achieved have been proven to have placenta praevia.

Ultrasonic placentography was unsatisfactory in three cases and repeat examination advised, but the placenta was located in all cases.

Forty-four patients in the series had a degree of placenta praevia requiring delivery by Caesarean section (Table I). All presented with antepartum haemorrhage.

False-negative placenta praevia

In six of the patients who had false-negative isotopic placentography, an ultrasonic examination was done and placenta praevia was shown in five of them. In retrospect it was felt that an error of interpretation had been made in three of the false-negative isotope placentograms, all of which were investigated early in the series. Two of these would now be regarded as frank placenta praevia. In the third patient the placenta was bilobed, and the inferior lobe was mistaken for the bladder. Eight cases (18%) remained falsely negative.

The two false negative ultrasonic placentograms were also reviewed. One of these had scans at 28, 30 and 36 weeks. The first scan suggested an upper segment placenta, the second a Grade IV placenta praevia and the last scan an anterior wall upper segment placenta. On review no evidence of placenta praevia was seen on this scan. Clinically it proved to be a Grade III placenta praevia.

The other patient examined early in the series had a twin pregnancy with separate placentas, one on the upper posterior wall and the other a central placenta praevia. This case was the one of the false-negative isotope placentograms referred to above. This was the only placenta praevia overlooked by both techniques.

TABLE II

ACCURACY OF SCANS COMPARED WITH FINDINGS AT CAESAREAN SECTION

Placental site confirmed at Caesarean section	36
Both scans in agreement and accurate	21
Ultrasonic scan more accurate	9
Isotope placentogram more accurate	5
Neither scan accurate	1

False-positive placenta praevia

Five (1.7%) of the isotope placentograms and ten (5.7%) of the ultrasonic placentograms were falsely positive.

In three of these an upper segment placenta was found at Caesarean section. In the remaining seven cases vaginal delivery occurred without significant blood loss or other evidence of placenta praevia.

In 36 of the patients who had isotopic and ultrasonic placentograms the placental site was recorded at Caesarean section (Table II).

DISCUSSION

The overall accuracy of placental localization assessed by numerous methods is said to be between 95% and 100% (Aiers *et al.*, 1969; Mishkin *et al.*, 1970; Wright, 1970; Kukard and Freeman, 1973). However, in the great majority of patients investigated, the placenta lies in the upper segment in which situation minor inaccuracies of localization are tolerated and not usually recorded as errors. On the other hand in the minority of patients who have lower segment placentas accurate localization is much more important because failure to recognize the condition may be dangerous (Kukard and Freeman, 1973). In the present series there were 44 proven placenta praevias of major degree of which 18% were not diagnosed by isotopic scanning and this is a surprisingly high percentage. However, it is not significantly different from the error rate of other large series when the results are pooled (Table III). It is slightly higher than the 13% error rate estimated by Johnson and King (1974). The main cause of this high error rate is the difficulty of

TABLE III

ERROR RATE IN REPORTED ISOTOPIC PLACENTOGRAMS

Series		Total scans	Placenta praevia	False negative	% false negative
Johnson *et al.*	1972	100	23	3	
Kohorn *et al.*	1969	50	?	0	
Niehoff *et al.*	1970	16	4	1	
Cohen *et al.*	1972	41	5	1	
Smith *et al.*	1970	96	6	0	
Wright	1970	200	26	1	
Aiers *et al.*	1969	62	10	2	
Kukard and Freeman	1973	155	58	12	
Mishkin *et al.*	1970	?	15	1	
		720	147	21	(14%)
Present	1975	290	44	11	(25%)
Total		1010	191	32	(17%)

*Error rate on review = 18% (see results).

defining accurately the limits of the lower segment of the uterus on the isotope scan. The cervix and internal os usually lie deep to the symphysis pubis and total placenta praevia can be judged fairly accurately from anterior-posterior projection. Lesser degrees of placenta praevia are more difficult to judge from anterior-posterior projections alone and a lateral projection is needed as well. The position of the cervix is more variable in lateral view (Johnson and King, 1974) and bony landmarks (Wright, 1970) are not entirely satisfactory. The use of a vaginal radioactive marker to locate the cervix (Rosenthall, 1969) is not generally acceptable. Other causes of error occur less commonly. For example urinary activity in the bladder, though uncommon, can be confused with a low-lying placenta but this is an uncommon cause of error. Usually this gives rise to a false-positive diagnosis but in one of the present series a low-lying lobe of a bilobed placenta was mistaken for the bladder because there was a recognizable placenta in the upper segment. At the time of the examination the radiologist was unaware of the diagnosis of twin pregnancy. Had this been known the suspicion of a bilobed placenta would have been raised. Finally on rare occasions an apparently fundal placenta turns out to be in the lower segment (Wright, 1970) and the disparity is inexplicable.

False-positive diagnosis of placenta praevia by isotope methods occurs in about 4% of cases (Johnson and King, 1974) and urinary activity in the bladder is an important contributor that can usually be excluded by good technique and experience. Occasionally vessels in the broad ligament and pelvis can be shown by high performance gamma-cameras. Their recognition has the advantage of identifying the lower segment. Should they be abnormally dilated they may be confused with succenturiate placenta (Connolly and Schokman, 1971).

In most series the final decision on placental location is taken after reviewing the results of labour, including post-partum assessment of placental site, or its direct visualization at Caesarean section. Dextro-rotation of the uterus during pregnancy (Kohorn *et al.*, 1969) may account for some discrepancies but it is unlikely to account for more than a small proportion of inaccurate results. Even when allowances are made for such an error, and also for technical expertise and experience, it is clear that there is an inherent error in the isotope method of detecting placenta praevia of the order of 17%. This error is proportionally decreased if the results are expressed for all patients examined but it is unacceptably high for patients with placenta praevia.

The accuracy of ultrasonic scanning is much higher, and the false-negative placenta praevia rate in reported series has ranged from 13.3% (Donald and Abdulla, 1968) in earlier series to 3.2% more recently (Kukard and Freeman, 1973). Similarly false-positive placenta praevia rates of 4.1% and below have been achieved (Campbell and Kohorn, 1968). In the present series ten false-positive diagnoses of placenta praevia were made out of 175 examinations and thus the ultrasonic method tends to over-diagnose the condition. It is essential to ensure that the bladder is really full to localize the placenta accurately in the lower segment. In some of the early cases in this series, this was not the case. When the placenta is on the anterior uterine wall, it is easier to outline its limits than if it is posterior in position and thus a mis-diagnosis of anterior placenta praevia is unlikely. When the placenta is posterior in position, scattered echoes behind the presenting part, particularly the fetal head, can obscure the lower edge and lead to a false-positive diagnosis.

Laterally re-scanning after light external pressure on the presenting part has been used to demonstrate whether the space behind it can be reduced or eliminated. If so, the presence of the placenta behind it can be excluded and actual limits of the placenta defined more precisely. False-positive diagnosis is unlikely too if the placenta is laterally placed. Confusion with echoes from a limb between the presenting part and the internal os has also occasionally been a cause for a false diagnosis of a major degree of placenta praevia.

The greater accuracy of ultrasonic scanning is due to its ability to define the placenta accurately and to relate the placental margin to the positions of the presenting part of the fetus and the internal os. This ability is sometimes limited only when the gestation is less than 34 weeks, when a poorly defined lower segment and a relatively high presenting part may lead to over-diagnosis of placenta praevia. The superiority of ultrasonic localization over isotopic localization is confirmed in other recent series. For example a false-negative rate of 3.2% (ultrasonic) is far better than one of 21% (isotopic) in 58 cases (Kukard and Freeman, 1973) and is a considerable improvement on earlier results where both methods were inaccurate (Aiers *et al.*, 1968).

Both methods show some inaccuracies compared with surgical localization of the placenta (Table II) and a similar discrepancy has been noted by others (Kohorn *et al.*, 1969). However, the section was not done for placenta praevia in all these cases (Table II) and the disparities reflect the greater tolerance of inaccuracies in the upper segment, as well as possible rotation of the uterus during pregnancy (Kohorn *et al.*, 1969).

The superiority of ultrasonic placentography over isotopic placentography is established beyond doubt. It was advocated at one time that ultrasonic placentography should be the method of choice in large units where technical expertise was available and isotopic placentography should be used in smaller units (Kohorn *et al.*, 1969). Our recent experience suggests that there is an irrefutable case for advocating that ultrasonic placentography should be available to all maternity units.

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Treatment of locally advanced prostatic carcinoma

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ABSTRACT

An analysis of 66 patients with prostatic carcinoma treated by telecobalt therapy more than two years ago shows that this can be curative in a high percentage of cases. Local failure occurred in 20.5%. Well-differentiated tumours are more radiosensitive. Clinical regression can take a long time and histology can remain positive for even longer in an inactive prostate gland. A high dose is however required. The use of oestrogens should be delayed until further treatment is needed, as oestrogen seems to increase the radioresistance of the tumour. Radiotherapy seems to be the treatment of choice in inoperable (and even operable) patients with carcinoma of the prostate limited to the pelvis.

Only about 5% of all patients presenting with prostatic carcinoma are medically or surgically suitable for radical curative surgery (Flint and Hsiao, 1967). The vast majority are not curable by means of surgery alone owing to local spread of the tumour in the capsule and periprostatic tissues. Some patients present with metastatic disease, while the general condition of others rules out radical surgery. One also meets patients who are not able to face such a procedure, due to the unavoidable impotency. In South Africa, prostatic cancer is the second most common malignancy in white males (Bradshaw and Harington, 1975). A similar incidence is found all over the world (Corriere *et al.*, 1970). Consequently there are a vast number of patients with locally advanced disease, without metastatic spread beyond the pelvis, who require help.

Radiotherapy was tried early in the century, but results were very disappointing, and this modality fell in disrepute. In the early '40's it was noted that a high percentage of prostatic carcinomas regressed when the patients were given oestrogens (Huggins and Hodges, 1941; Herbst, 1942). This breakthrough was accepted throughout the world with immense relief, and was applied everywhere. Despite early reports that this modality was not a complete panacea (Andersen, 1950; Gahagan and Fischman, 1949), all inoperable patients with cancer of the prostate were manipulated with hormones. One big disadvantage was that most carcinomas escaped from the oestrogenic control. In 1967 the Veteran's Administration Group published results showing that the average survival of patients treated with oestrogens was no longer than that of patients who did not receive oestrogens. The difference, however, was in the cause of death, being due to cancer in the second group, while the first group had a much higher incidence of thrombo-embolitic incidents with fatal results.

Over the past few years an increasing number of reports have appeared showing that very useful results can be obtained with modern radiotherapy (Ray *et al.*, 1973; Rodriguez-Antunez *et al.*, 1973; Hill *et al.*, 1974; de Mûelenaere *et al.*, 1974). The difference from the early reports is due to the fact that a higher tumour dose can be given with modern apparatus.

MATERIAL

Our department has actively advised radiotherapy for patients with carcinoma of the prostate since 1967. Our technique has already been published (de Mûelenaere *et al.*, 1974). Our therapy is based on that used for bladder cancer. A telecobalt unit is used and four fields at 45, 135, 225 and 315 deg. are treated daily, five days per week. The field sizes are mostly 9 × 9 cm^2 and are aimed at the depth of the 50% contour below the symphysis pubis. We originally gave a tumour dose of 5 130 rad in 20 treatments over 26–28 days. This dose was later increased to 5 415 rad in 20 treatments in four weeks. We have now changed to a split course technique, where 2 850 rad is given in ten treatments over 12–14 days, then a rest period of 2–2½ weeks, after which another 2 850 rad is given in ten treatments over 12 days. When these doses are expressed as TDF factors (Orton and Ellis, 1973) the original dose gives a TDF of 96, 5 700 rad in four weeks gives 105 and 6 000 rad as a split course equals 107.

It must be emphasised that our patients were not selected; all patients were treated. The stage of the disease varied, but the overwhelming majority were in stage B$_2$ or C. Several of the patients had been given oestrogens for shorter or longer times (six months to ten years) before being referred to us when there was proof of reactivation of the tumours. Other patients were treated by radiation immediately after diagnosis, and of these some received oestrogens concomitantly whereas others did not, depending on the referring urologist. We give oestrogens during radiotherapy only when the urologist specifically asks for it as we ourselves are not in favour of routine oestrogen administration. It must be stressed that no clinical condition except secondaries outside the pelvis was considered by us to require the administration of oestrogens.

A total of 66 patients were treated between 1967 and 1973, with a minimum follow up of two years. The average age of these patients was 66 years when registered for radiation, whereas the median age was 70 years. These ages were not those at the time of diagnosis, as a number of the patients had received oestrogens before they were referred to us.

RESULTS

An interesting finding is that 30 of these patients, *i.e.* almost half, developed secondaries. The time at which these metastases were diagnosed varied from before treatment by radiotherapy to 30 months afterwards. Of the original 66 patients, 40 have died. The time of demise varied between one month and 46 months after radiation. Eleven of the 40 deaths were from thrombo-embolitic events. As can be seen in Table I, ten of these had been on oestrogen therapy. Ten out of 34 patients who were given oestrogens had fatal vascular incidents, compared to only one out of 32 patients who did not take oestrogens. This was one of two patients who developed multiple pulmonary embolisms. The difference in thrombo-embolitic incidence between these two groups is remarkable and statistically significant. The patients who died did so on average 17½ months after radiotherapy, or at a median survival time of 18 months. Because some patients were referred long after the diagnosis was made, the average and median survival after diagnosis in the patients who died is 34 and 24 months respectively (Table II). Although the median survival for the whole group cannot be computed as some were treated only 24 months ago and are still alive, it seems as if the median survival of the whole group will be in the region of 36 months.

TABLE I

THROMBO-EMBOLITIC DEATHS

Oestrogen	Number	Total	%
Yes	10	34	29.4
No	1	32	3.1
Total	11	66	16.7
$P < 0.01$			

TABLE II

SURVIVAL TIMES OF THE 40 PATIENTS WHO HAVE DIED

After RT	Average	17.7	months
	Median	18	months
From diagnosis	Average	34.3	months
	Median	24	months

After radiation, biopsies were taken of the prostate in 43 patients, on more than one occasion in most of them. An important finding was that in several patients these needle biopsies remained histologically positive for carcinoma, despite the clinical finding of an inactive tumour. The longest time interval after radiation where the biopsy was still positive was 36 months, whereas it was negative in this same patient at 44 months.

The clinical regression after radiation is usually very slow, and can take between six and nine months. Of all the cases that became locally active again, only in one patient did the tumour become active more than two years after radiation. Because of the inaccuracy of the biopsies, and due to the fact that clinical activity can recur after a long time, all patients who survived at least two years were analysed separately. Only clinical proof of activity was considered. Of the original group 27 died less than two years after radiation, leaving 39 cases for analysis. Of these eight developed activity, an incidence of 20.5%.

The following analysis was made to determine what factors are important in affecting the radiosensitivity of prostatic cancer. In Table III histological differentiation is considered. It can be seen that moderately and poorly differentiated tumours are less radiosensitive than well differentiated

TABLE III

HISTOLOGICAL DIFFERENTIATION

	Active	Not active	Total	%
Well differentiated	0	13	13	0
Moderately differentiated	1	2	3	33.3
Poorly differentiated	4	6	10	40
Differentiation unspecified	3	10	13	23
Total	8	31	39	20.5
$0.05 > P > 0.02$				

carcinomas. This difference is of statistical significance. A number of patients received oestrogens before radiation; the effect of this is analysed in Table IV. It can be seen that the tumours in patients who did receive oestrogens had a greater tendency to become active again. This difference is not statistically significant. The effect of oestrogen given concomittantly with radiation is analysed in Table V. It is clear that patients who did receive oestrogen did worse, and not better, although once again this difference is not statistically significant. In Table VI the effect of the dose of radiation is considered. The tumour dose is expressed as TDF factors as suggested by Orton and Ellis (1973). It can be seen that all cases whose tumours became active again had received lower doses. This difference is of statistical significance.

TABLE IV

EFFECT OF PRIOR OESTROGEN

Prior oestrogen	Active	Not active	Total	%
Yes	6	14	20	30
No	2	17	19	10.5
Total	8	31	39	20.5
$0.20 > P > 0.10$				

TABLE V

OESTROGEN WITH RADIATION

	Active	Not active	Total	%
Yes	6	13	19	31.6
No	2	18	20	10
Total	8	31	39	20.5
$0.10 > P > 0.05$				

TABLE VI

RADIATION DOSE

T.D.F.	Active	Not active	Total	%
<100	8	19	27	29.6
>105	0	12	12	—
Total	8	31	39	20.5
$0.05 > P > 0.02$				

DISCUSSION

Our findings confirm that prostatic carcinoma is not an innocuous disease. Our experience also shows that oestrogen therapy has its inherent dangers. It is exactly because of these two factors that we recommend radical radiotherapy in all patients who have locally advanced disease with no secondaries outside the pelvis. Oestrogen should be withheld until there is definite proof of secondaries causing symptoms. For widespread disease, palliative radiotherapy can be given with a lower dose to relieve symptoms of obstruction.

Our previous report (de Mûelenaere *et al.*, 1974) showed an incidence of severe complications, *e.g.* bladder constriction, in only 5% of patients, which we find acceptable in such a serious disease. Local control of the disease was obtained in almost 80% of all cases, including those where radiotherapy was not optimal. We think this is a very gratifying result.

Follow-up needle biopsies are not very reliable, as has been pointed out before (Rodriguez-Antunez *et al.*, 1973). It must be kept in mind that regression of tumour can be very slow, as has been described previously (Ray *et al.*, 1973). Recurrence of local growth is usually found within two years. The degree of differentiation of prostatic tumours seems to influence radiosensitivity, with the well differentiated carcinomas responding better. Fortunately the majority of tumours are well differentiated. It is of course possible that the well differentiated tumours recur later.

It seems to be deleterious to combine radiotherapy with oestrogen, whether these are given before or concomitantly with the radiation. Radiation should thus be given as the first line of attack. Table V confirms that the beneficial effect was in fact due to the radiation and not to hormonal manipulation. Oestrogens definitely increase the risk of thromboembolitic incidents. There are therefore two reasons why oestrogens should be withheld until required by the development of secondaries. It has been shown that the hormonal *milieu* may influence the radiosensitivity of certain tumours, *e.g.* endometrial carcinoma (de Mûelenaere, 1975). The same principle seems to apply to prostatic cancer, in that oestrogens make the tumour more radioresistant. Our figures are not definite proof as they are not statistically significant, probably due to a paucity of numbers.

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Book review

Traite de Radiodiagnostic. Tome XI: Rhumatologie, Articulations, Parties molles. By R. Trial, M. Laval-Jeantet and M.Chr. Plainfossé, 464 pp. with 545 illustrations and different colourplates, 1976 (Masson – Paris), 540F.

Rhumatologie, Articulations, Parties molles represents part XI of the French *Traité de Radiodiagnostic.*

The first section (68 pages) covers the morphological and biological basis of articular pathology as well as a remarkable chapter on arthroscopy (with beautiful colour plates) and some technical aspects and new developments in osteo-articular radiology.

The second section (221 pages) is devoted to the radiodiagnosis of articular and periarticular diseases. It provides, in a concise manner, a complete view of common and rare articular conditions. A minor criticism concerns the covering of Reiter's disease where the lesions of the vertebral column are not mentioned.

The third section (52 pages) deals with arthrography of the shoulder, elbow, wrist, hip, knee and ankle. Basic information concerning technique, normal anatomy and pathological findings is provided for each of these methods and although it will not replace the need for monographs on these topics, it will be most useful as an introduction for anyone learning these methods.

The last section (83 pages) covers the radiography of the articular and periarticular soft tissues as well as of the muscles and the skin.

This is a most original and remarkable section. New ideas and technical developments concerning radiography of the soft tissues are here developed and nicely supplemented by drawings and pertinent radiographs. It provides a totally new view of a field that has been too much neglected in the past.

Printing and radiographs are, as usual in this prestigious French handbook, of superb quality. An up-to-date bibliography is given after each chapter.

This book can be recommended for each medical or radiological library. It should prove an excellent work for medical students and residents and a valuable aid for each radiologist in charge of teaching.

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Measurement of ^{57}Co-vitamin B_{12} uptake using a static whole-body counter

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Abstract

Using a whole-body counter which incorporates eight static NaI((Tl) detectors, it has been found possible to measure the absorption of vitamin B_{12} labelled with ^{57}Co instead of ^{58}Co, with a consequent reduction in absorbed radiation dose to the patient.

The use of whole-body counters for the measurement of vitamin B_{12} uptake in humans is well established. Vitamin B_{12} used for this purpose is normally labelled with ^{58}Co (predominantly 0.81 MeV γ rays, $T_{\frac{1}{2}}$ 71 days). However, it is preferable to use ^{57}Co (predominently 0.12 MeV γ rays, $T_{\frac{1}{2}}$ 270 days) for this purpose, because the cumulative radiation dose to the liver is lower ($\sim$ 280 mrad per μCi in the liver) as compared with approximately 450 mrad per μCi for ^{58}Co.

It is generally considered that the low γ-ray energy of ^{57}Co makes it unsuitable for the measurement of vitamin B_{12} uptake using a static NaI(Tl) crystal whole body counter, owing to large variations in sensitivity with distribution in the human body (Mollin, 1962; Heyssel, 1966; Reba and Wagner, 1969). However, ^{57}Co can be used either with scanning-type counters incorporating NaI(Tl) crystals (Naversten, 1966; Boddy *et al.*, 1969) or with static counters having approximately 4 π geometry (Cohn *et al.*, 1969).

The studies reported here show that contrary to expectation it is in fact possible to measure whole body retention of ^{57}Co vitamin B_{12} with adequate accuracy using a static whole body counter with eight NaI (Tl) crystal detectors.

Whole-body counter

The whole-body counter is a multi-detector facility situated inside a low-background shielded cubicle (steel, thickness 15.2 cm). Eight detectors are positioned so that four are above, and four are below the supine patient (Fig. 1). The faces of the upper detectors are 35 cm above the couch, and the faces of the lower detectors are 5 cm below the couch. Each detector incorporates a NaI(Tl) crystal 10.2 cm diameter × 7.6 cm thick.

The average background count rate (B) measured with a distilled water phantom in position was 380 counts min^{-1} in the energy range 0.06 to 0.18 MeV. Corresponding count rates from adult patients (*i.e.* subject plus background (S+B)) varied from 432 to 541 counts min^{-1}, with mean values of 479 c.p.m. (SD38, n=9) for males and 453 c.p.m. (SD14, n=8) for females. The average counting sensitivity for ^{57}Co in patients was 16 500 counts min^{-1} per μCi, measured one hour after swallowing a vitamin B_{12} capsule labelled with ^{57}Co (approximately 0.5 μCi ^{57}Co).

Two detectors of the whole-body counter, positioned one above the other, with faces 40 cm apart, were used to measure the amount of ^{57}Co in each capsule, and in each subsequent stool sample. The sensitivity for counting ^{57}Co in this sample counting geometry was approximately 54 000 counts min^{-1} per μCi (0.06–0.18 MeV) with a corresponding average background of 93 counts min^{-1}.

Patients and Methods

The patients had either presented with megaloblastic anaemia, or were suspected of malabsorption due to resection of the ileum. One person was a normal adult male member of staff.

Each person fasted overnight and was then measured in the whole-body counter for 400 sec to determine the individual background (S+B).

A capsule containing ^{57}Co-labelled vitamin B_{12} (0.5 μCi+1 μg vitamin B_{12}, Radiochemical Centre, Amersham), which had previously been measured in the sample counting geometry, was then swallowed with a drink of water. No vitamin B_{12} blocking doses were given.

Measurements of body radioactivity were made after one hour and at about seven days later in each case, for counting times of 400 sec. Additional measurements were made, whenever possible, immediately after the capsule was swallowed, and after three and six hours, in order to assess the variations in sensitivity which occurred during the first six hours.

Complete collections of stool samples were obtained from seven patients in a metabolic ward, and from one normal male, so that uptake measured by whole-body counting and stool collection methods

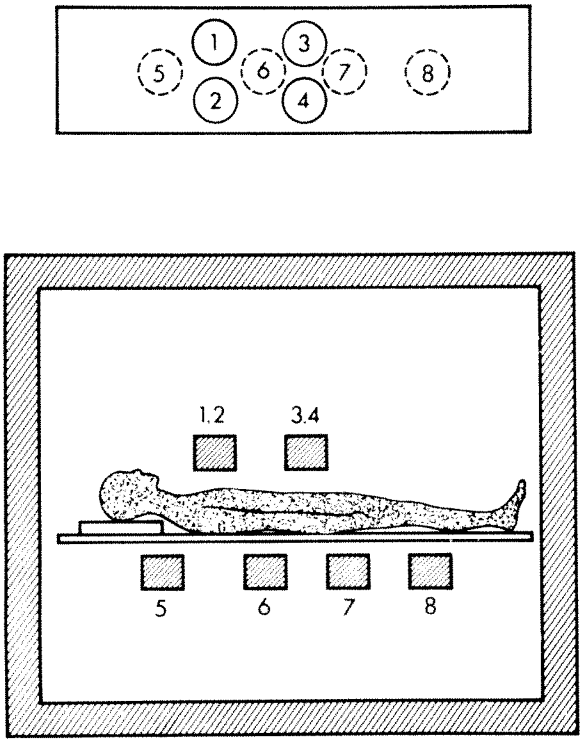

FIG. 1.
Whole-body counter; patient detector geometry.

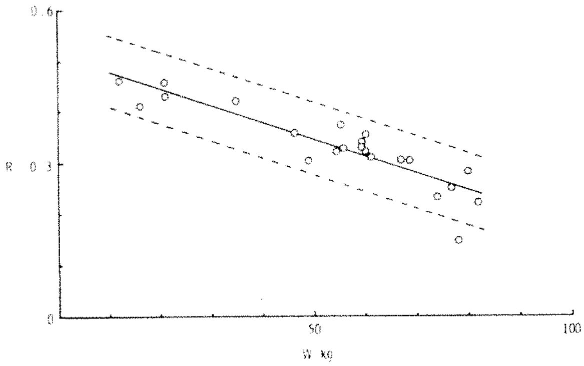

FIG. 2.
Regression of R upon body weight (W). (95% confidence limits are shown.)

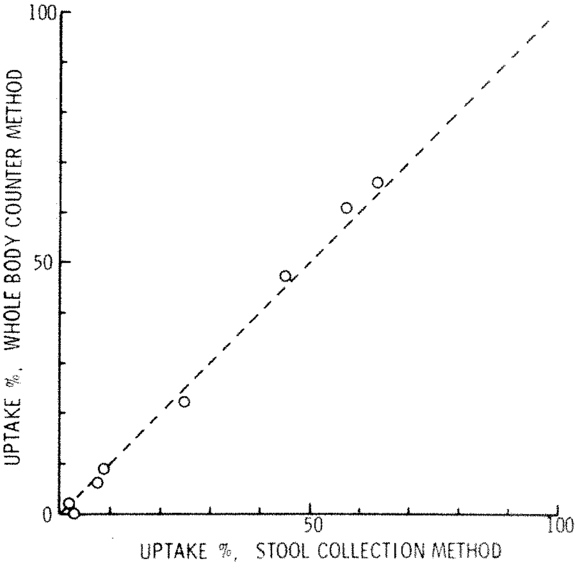

FIG. 3.
Relationship between whole-body counter and stool collection methods for determining ^{57}Co-vitamin B_{12} uptake (line of identity is shown).

could be compared. Stool samples were collected in sealed plastic tubs (Mono Containers Ltd., capacity 0.5 l) and the ^{57}Co content measured in the standard counting geometry.

RESULTS

Count rates from ^{57}Co in the body during the first six hours after swallowing the capsule are presented in Table I, expressed as a multiple of the count rate at one hour. The ratio (R) for the one-hour ^{57}Co count rate from each patient, measured in the whole-body counter, to the count rate from the corresponding capsule, measured in the sample counting geometry, varied with the body weight (W, kg) of the patient (Fig. 2). The regression of R upon W was defined by the following equation:

$R = 0.51 - 0.0033\ W$

S.D. about regression ± 0.036

r (coefficient of correlation) $= 0.90$ ($n = 22$, $p < 0.001$).

Values for the uptake at seven days measured by whole body counter, using the one hour count rate as the 100% value, were compared with the uptake measured by stool collection (Fig. 3). The difference between each value for the uptake measured by whole body counter and the corresponding value measured by stool collection was calculated. The mean value of these differences was 0.36% (S.E.M. 0.81%, $n = 8$) of the dose administered.

DISCUSSION

The average count rate from ^{57}Co in the body was relatively constant between one and six hours after swallowing the capsule (Table I), while large variations occurred during the first hour.

A comparison between uptake at seven days as measured by whole-body counter, using the one

TABLE I

Relative count rates from ^{57}Co in the body at various times after administration

Time (hours)	0	1	3	6
Mean	1.25	1.00	0.98	1.04
Range	0.76–1.97	—	0.85–1.06	0.87–1.29
S.D.	0.42	—	0.11	0.16
n	13	17	4	6

hour measurement as the "100%" value, and the stool collection method (Fig. 3), indicated that there was good agreement between the two methods.

As the whole-body counter method does not require the collection of stool, urine or blood samples, it is ideally suitable as an out-patient procedure. For the same reasons it is a method suitable for the determination of vitamin B_{12} uptake in infants and children.

Provided that the ^{57}Co capsule is measured prior to administration, it is possible to measure vitamin B_{12} uptake even in the absence of a one hour count on the patient, since the one hour count rate can be estimated from the correlation of R upon W (Fig. 2). Thus only one whole-body count, on day seven is required to re-assess an inconclusive result obtained by the eight hour plasma method (Cottrall *et al.*, 1971), which is used routinely in this hospital. The resulting standard error, due to counting statistics and the uncertainties in R and (S + B), on an uptake of 10%, is approximately ±1.4% of the administered dose.

When the patient's normal body radioactivity and the one hour ^{57}Co count rates are measured, the standard error due to counting statistics on an uptake of 10% is approximately ±0.2% of the administered dose, for counting times of 400 sec on each occasion. If the administered dose is reduced to 0.1 μCi ^{57}Co, the corresponding error is only increased to ±0.8%, and the cumulative radiation dose to the liver is reduced by a factor of five. For an uptake of 50%, which would be associated with that for normal adults (26–87%, Mollin *et al.*, 1957), the cumulative radiation dose to the liver would be reduced to about 14 mrad.

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The spectrum and intensity of extra-focal (off-focus) radiation

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ABSTRACT

Conflicting results have been obtained by other workers for the quality of radiation originating outside the area of the focal spot on X-ray tubes. This extra-focal radiation results in poorer picture quality, especially in cases where grids are not being used. As part of an investigation to assess the importance in diagnostic radiology of the various factors affecting the output from X-ray tubes, the photon spectrum has been examined using a Ge(Li) detector. The measured spectra have been adjusted for the effect of the detector characteristics.

Results show that the extra-focal radiation is softer than that from the focal spot and, for the X-ray generator measured, constitutes approximately 8% of the exposure at 100 kV with a total filtration equivalent to 2 mm of aluminium. The possibility of further collimation to reduce this component, thus improving picture quality, is considered.

This work is concerned with the measurement of extra-focal radiation, and is part of an investigation into the parameters affecting X-ray tube output in an attempt to assess their importance in diagnostic radiology. The radiation produced from an X-ray generator does not all originate from the focal spot. Particularly in modern tubes with rotating anodes there is quite a large contribution to the exposure from extra-focal radiation. Ardran *et al.* (1964) found the magnitude of this contribution to be approximately 10% of the total exposure with 60 kV across the tube and the makers lead collimator in position.

The extra-focal radiation results in impaired picture quality, particularly for example in chest radiography where a grid is not used (Ardran *et al.*, 1964). It will also result in unnecessary patient dose and introduce an error into the measurement of the half-value layer (HVL) of the useful beam. Collimation, additional to that of the manufacturers, placed as close as possible to the X-ray tube, as mentioned by Ardran (1957), would reduce this component.

Conflicting results have been obtained in the past concerning the quality of the extra-focal radiation. Mallet and Maurin (1947) measured half-value layers on a Picker mobile X-ray generator and concluded that the extra-focal radiation was more penetrating. More recently Jackson (1975) has reported that measurements using a penetrameter suggest that it is softer, which was also found by Ardran and Crooks (unpublished) using the same method.

This paper presents measurements of the spectra and magnitude of extra-focal X-rays and discusses whether attempts to reduce their intensity are worthwhile.

EXPERIMENTAL TECHNIQUE

To measure the radiation emitted from small areas of the target a shortened version of the spectrometry collimating system reported previously by Peaple and Burt (1969) was used. This consists of three lead collimators (pinholes) set at known distances apart permitting only a narrow beam of radiation to hit the detector. For the present investigation the beam half-angle at the detector is 0.075°, so that with an air path of one metre between the detector and the tube window, radiation is received from 5.4 mm^2 of the anode (a circle of diameter 2.62 mm). Different regions of the anode can therefore be observed, the position relative to the focal spot being indicated by a system of pointers and scales (marked in 0.5 mm divisions). The area of the anode visible at a point one metre from the focal spot, with the manufacturer's collimation in position, is shown in Fig. 1B. The dimensions were verified by a pinhole photograph. The position of the additional collimator is shown in Fig. 1A and it can be seen that this collimator significantly reduces the visible area of region 1. The detector was a Ge(Li) planar crystal, 10 mm diameter by 8 mm deep, having a gold

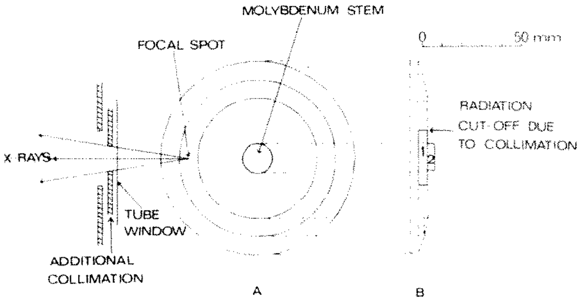


FIG. 1.

(A) Diagram of rotating anode (as viewed from cathode), showing position of additional collimation.

(B) Areas of the anode and stem from which radiation is received at a point one metre along the beam axis, with the manufacturer's collimation in position for the Gigantos generator (viewed along the beam axis).

surface layer of thickness 0.04 μm. The pulses from the detector were analysed with an analogue to digital converter (AERE type 0319), the data being stored using a 1024 channel digital processor (Geoscience type 7000) before subsequent transfer to paper tape.

It was necessary to adjust the measured pulse height distributions for detector characteristics, using a "stripping" technique to determine the true photon spectrum incident on the detector. The response matrix takes account of the escape of Ge K X-rays, loss of Compton scattered photons and transmission through the crystal (Peaple and Marshall, to be published).

Exposure rates at the detector, due to radiation from specific areas of the target, were calculated from the photon spectra after correction for dead time.

By calculating the mean exposure rates from unit area of regions 1 and 2 of Fig. 1B, together with the areas calculated for these regions, the exposure rate at the detector due to all radiation except that from the focal spot can be estimated.

Results

Measurements were carried out mainly on a Siemens Gigantos X-ray generator, using the 10° target angle of the bi-angulix tube, at 50 kV and 100 kV. The generator is full-wave rectified (12 pulse) with a three-phase supply.

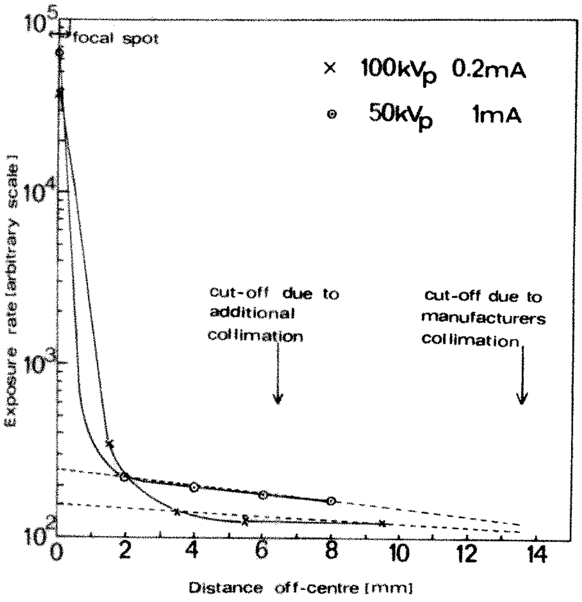
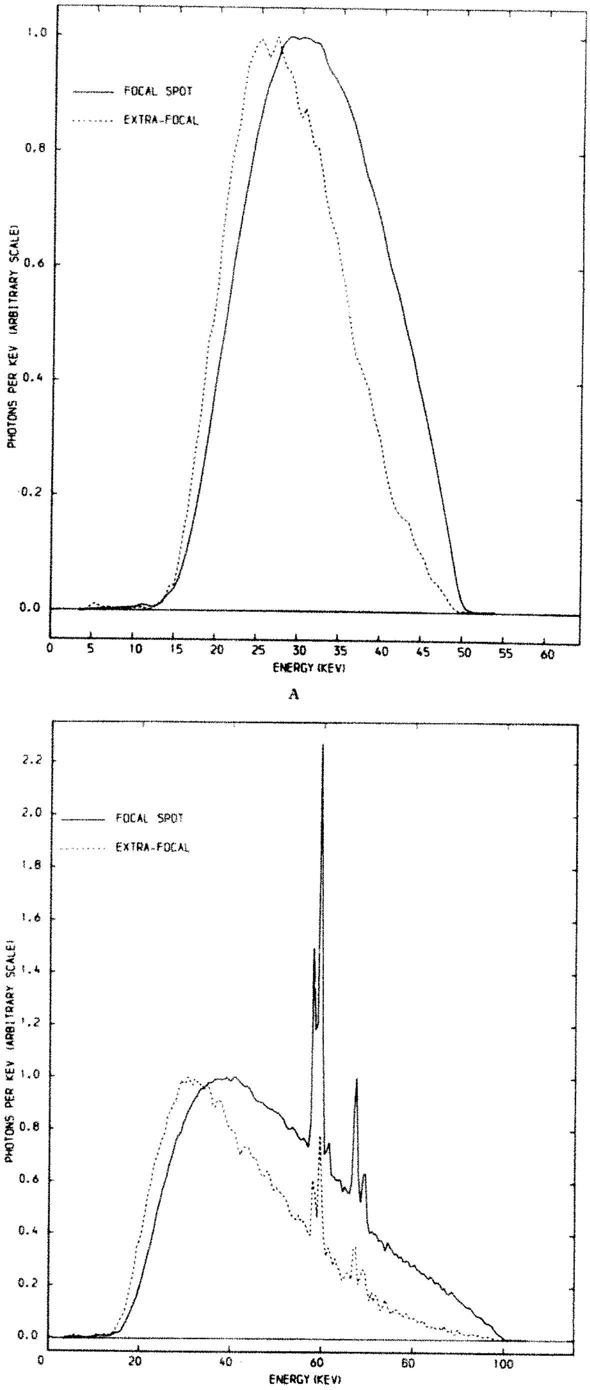


Fig. 2.

Variation in exposure rate with distance perpendicular to the anode–cathode direction, for the Gigantos generator.



A

B

Fig. 3.

Comparison of radiation from the focal spot of the Gigantos generator with extra-focal radiation at (A) 50 kV 1 mA (4 mm off-centre) and (B) 100 kV 0.2 mA (3.5 mm off-centre) in a direction perpendicular to the anode-cathode direction. (The spectra have been normalized to a value of 1.0 at the maximum of the continuous distribution.)

The variation in exposure rate from areas at increasing distance away from the focal spot in a direction perpendicular to the anode–cathode direction is shown in Fig. 2. The measurement obtained at a distance of 1.5 mm off-centre at 100 kV may include a small amount of the focal spot resulting in a high reading, and so this value was not included in the extrapolation. Examples of the spectra obtained in this direction are shown in Fig. 3.

The exposure rate from areas in the anode–cathode direction (the stem region) did not vary greatly and was 1.6×10^{-3} and 2.4×10^{-3} times that of the focal spot at 100 kV, 0.2 mA and 50 kV, 1 mA respectively. The photon spectrum from this region is shown in Fig. 4 with molybdenum K X-rays (17.4 and 20.0 keV) from the molybdenum stem.

Measurements were also made on a Picker mobile X-ray generator (half-wave rectified) with a total filtration equivalent to 1.5 mm of aluminium. These spectra are not included as they were very similar to those obtained from the Gigantos generator.

The variation in mean exposure energy and HVL for increasing distance from the focal spot (in a direction perpendicular to the anode–cathode direction) are shown in Table I. Estimates of the percentage of the total exposure due to extra-focal

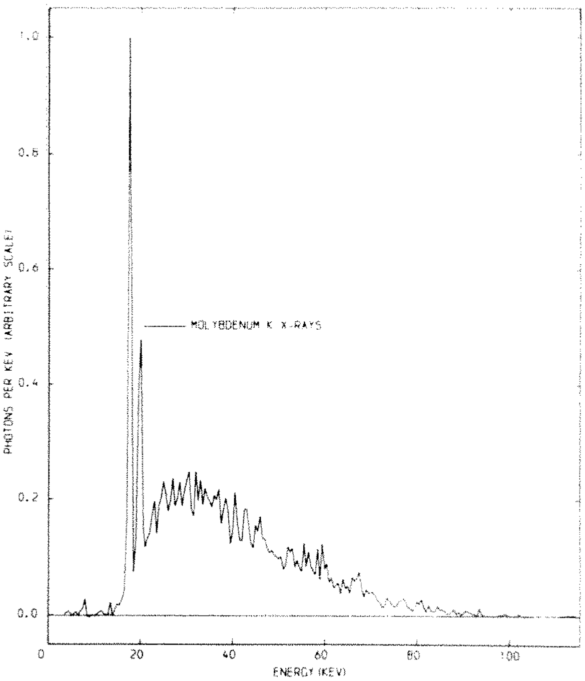


Fig. 4.

Extra-focal radiation (100 kV, 0.2 mA) from the top of the anode stem, 4 mm off-centre in the anode–cathode direction of the Gigantos generator.

TABLE I

Variation in mean exposure energy and HVL with distance from the focal spot

(a) Gigantos X-ray generator (2 mm Al total filtration)				
Distance* (mm)	Applied voltage			
	50 kV		100 kV	
	Mean exposure energy (keV)	HVL (mm Al)	Mean exposure energy (keV)	HVL (mm Al)
0.0 (central)	27.9	1.61	42.2	3.47
1.5	—	—	34.1	2.17
2.0	25.1	1.25	—	—
3.5	—	—	33.5	2.12
4.0	24.7	1.20	—	—
5.5	—	—	33.0	2.05
6.0	23.9	1.10	—	—
8.0	24.2	1.12	—	—
9.5	—	—	33.4	2.13
(b) Picker mobile X-ray generator (1.5 mm Al total filtration)				
Distance* (mm)	Applied voltage			
	35 kV			
0.0 (central)	21.65	0.84		
4.5	20.38	0.71		

*Perpendicular to anode–cathode direction.

TABLE II

PERCENTAGE OF TOTAL EXPOSURE DUE TO EXTRA-FOCAL RADIATION (GIGANTOS X-RAY GENERATOR)

Tube voltage kV	(a) with manufacturer's collimation	(b) with additional (12.5 mm diam.) collimation
50	6.5	3.9
100	8.0	4.8

radiation for the Gigantos generator are shown in Table II.

Due to the greatly reduced exposure rates from areas away from the focal spot the statistics of some of the spectra are poor, even though collection times were as long as twenty minutes. It was considered unwise to increase the tube current at a given voltage to improve the accumulation rate since the focal spot size is known to alter with this parameter.

With the spectrometry collimating system lined up in the central position the exposure rate at the detector is mainly due to radiation from the focal spot, but since the area observed (5.4 mm^2) is greater than the 0.6 mm × 0.6 mm focal spot a small proportion of the off-focus region is included. The error in the central measurement due to this poor resolution is small ($<1\%$) since the exposure rates for the central and off-centre positions are different by a factor of over a hundred. Although the exposure rates due to radiation from areas away from the focal spot are much lower, the total area from which extra-focal radiation is received by the patient is much greater than that of the focal spot, resulting in 8% of the total exposure at 100 kV being due to extra-focal radiation.

DISCUSSION

Figure 3A and B clearly show that the mean energy of the extra-focal radiation photon spectrum is lower than that of the focal spot. From Table I it can be seen that the mean exposure energy (or HVL) decreases away from the focal spot, but at approximately 8 mm from the centre the mean energy reaches a minimum and slowly increases again. In high atomic number materials, such as tungsten, nuclear scattering predominates over the scattering by bound electrons (Evans, 1955). Due to the large mass of the nucleus compared to that of the electron the back-scattered electron can have nearly the same energy as the incident electron independent of the angle of scatter. Close encounters between a fast electron and a tungsten nucleus may lead to sudden accelerations, resulting in bremsstrahlung radiation being emitted to conserve energy according to the laws of electrodynamics. This will result in the back-scattered electrons having a range of energies between zero and the energy of the incident electron. For any particular angle of back-scatter, the lower the energy of the electron the nearer it will be to the focal spot when it again hits the anode. The measured values therefore agree with the theory which indicates that the extra-focal radiation will have a lower mean energy (or HVL) than that from the focal spot. But the theory suggests that it should be lowest very near to the focal spot and should increase slowly with increasing distance away from the centre. Therefore there must be some other source, possibly unfocused electrons or electrons scattered by residual air molecules in the tube, hitting the anode close to the focal spot. Also X-rays may be scattered in the tube window such that they appear to have originated off-focus.

The percentage of the total exposure due to extra-focal radiation was 8% at 100 kV with the equivalent of 2 mm of aluminium total filtration on the Gigantos tube. With an additional square collimator of diameter 12.5 mm placed as close as possible to the X-ray tube this component would be reduced to 4.8%.

The extra-focal radiation from the Picker generator was softer than that from the focal spot, which is consistent with the theory and contradicts the results of Mallet and Maurin (1947).

Reduction of extra-focal radiation

It is clear that for some diagnostic procedures, particularly those using higher voltages, the extra-focal component of the exposure may be greater than 10% and additional collimation seems worthwhile. As has been shown an additional square collimator, placed as close as possible to the X-ray tube (on the Gigantos generator it is placed 36 mm from the focal spot) can reduce this component by approximately a factor of two. In all diagnostic procedures this would reduce unwanted radiation and improve picture quality. The improvement is most noticeable in techniques not using a grid, for example chest radiography using the air gap technique (Ardran, private communication), The size of the additional collimator should be such that the maximum field size is just obtainable under the geometry normally employed.

CONCLUSIONS

The photon spectrum of the extra-focal radiation has a slightly lower mean energy than that of the focal spot. The percentage of the exposure that is due to this extra-focal radiation increases with the voltage across the tube and, for the tubes measured, was 8% at 100 kV with 2 mm of aluminium equivalent total filtration. Additional collimation can reduce this component by approximately a factor of two resulting in improved picture quality and a reduction in unwanted radiation.

ACKNOWLEDGMENTS

This work, which was partly supported by the Biology Division of Euratom (Contract No. 128–74–1 BIO UK), was initiated by Dr. G. M. Ardran and Mr. H. E. Crooks and the author greatly appreciates their kind help and guidance. The author would like to thank Dr. M. Marshall, Mr. L. H. J. Peaple and Mr. J. A. B. Gibson for their suggestions and encouragement throughout this work.

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Book reviews

Cardiovascular Imaging and Image Processing Theory and Practice. Eds: Donald C. Harrison, Harold Sandler, and Harry A. Miller., pp. xiv + 360, 1975 (The Society of Photo-optical Instrumentation Engineers, California), $28.00.

The book is the contents of a three day meeting on the uses of ultrasound, x rays and isotopes in the investigation of the heart and vascular system. The contributions are from scientists, many from the United States space programme, physicians, and even from businessmen.

As one would expect from such an association there is much emphasis on the physical theory of image formation and data-processing in each modality, which limits the interest of some of the chapters, but all in all the book provides a reasonably up to date survey of the state of the art and a fascinating glimpse of the possible future of cardiovascular imaging.

MAURICE J. RAPHAEL.

Clinical Tests of Oesophageal Function. By Richard Earlham, pp. xiv + 383, illustrated, 1975 (Crosby Lockwood Staples, St. Albans, Herts), £12·00.

This is an excellent book which should prove of value to all those interested in gastroenterology. The author has achieved remarkable success in balancing clinical and experimental medicine and presenting it in a most readable fashion to the non-expert. The value of the physiological work which is now such an important aspect in the study of the oesophagus is discussed and related to the disease processes which may occur. Treatment and diagnosis of the common and rare oesophageal diseases are also adequately covered without unnecessary detail being given to medical and surgical treatment.

The book is extremely good value at this price.

J. A. GLEESON.

1976, *British Journal of Radiology*, 49, 956–962

An assessment of lithium borate thermoluminescent dosimeters for the measurement of doses to patients in diagnostic radiology

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ABSTRACT

A pilot survey of doses to patients undergoing four types of radiological procedure—barium enemas, intravenous pyelography, cardiac catheterization and mammography—has been made using lithium borate TL dosimeters. The survey was designed to test the operational suitability of the dosimetry system and to gain experience and gather data for the planning of further larger surveys.

The TL dosimeters were calibrated against conventional ionization chambers, and then used on patients for determining gonad doses and maximum doses to the skin.

Few difficulties were encountered in using the system. The measured doses to patients have been compared with previous determinations by other authors and reasonable agreement demonstrated.

This paper describes the results of a survey of the doses received by patients undergoing selected radiodiagnostic procedures at the Hammersmith and the Royal Surrey Hospitals. The survey was primarily intended as a pilot trial to determine the operational suitability of the dosimetry system, employing lithium borate thermoluminescent dosimeters, for use in larger surveys aimed at establishing the dose to the population of the United Kingdom from medical uses of ionizing radiation. The reasons for choosing this particular dosimetry system and a comprehensive description of its physical properties and performance have been given elsewhere (Langmead and Wall, 1976). It is also hoped that the doses measured for some of the procedures may be of more immediate use as an index of the effectiveness of the techniques employed at the two hospitals concerned for reduction of dose to the patient.

Doses to patients have been measured in four types of X-ray examination: (a) barium enemas; (b) intravenous pyelography; (c) cardiac catheterization and angiocardiography; and (d) mammography. Measurements were made at Hammersmith Hospital for examination types (a), (b) and (c) and at the Royal Surrey Hospital for mammography. Examination types (a) and (b) were chosen as examples of well-established procedures in the course of which the patients' gonads may be in the primary X-ray beam for a substantial fraction of the examination period. Consequently these examinations make a large contribution to the genetically significant dose to the population from medical X rays. Examination types (c) and (d) are more recent techniques about which only limited data are available on the dose received by the patient and where strenuous efforts are being made at the present time to reduce this to the minimum.

MEASUREMENTS ON A PHANTOM

The response of manganese-activated lithium borate powder per rad in soft tissue at the low energies used in diagnostic radiology was shown by Langmead & Wall (1976) to be no more than 10% greater than its response at energies around 1 MeV. In routine use the sensitivity of the powder is periodically checked by calibration with ^{137}Cs γ-rays and an appropriate correction factor is applied to take account of the difference in quality between the calibration radiation and the radiation that is to be measured.

As an additional check on the performance of the system prior to measurements on patients, dose measurements made with lithium borate powder were compared with measurements made with a 35 ml cylindrical ionization chamber connected to a Type 37C portable electrometer (Electronic Instruments Ltd).

Initially black polythene sachets of wall thickness 0.12 mm containing 30 mg samples of lithium borate and the 35 ml chamber were both calibrated against a secondary standard Baldwin Farmer dosimeter using a narrow beam of γ-rays from a conventional cobalt-60 therapy unit. Electronic equilibrium was established for both types of detector by surrounding them with an adequate thickness of Perspex.

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The 35 ml chamber was then irradiated on the surface of a Mix D phantom in the half-immersed position together with batches of five TLD sachets placed randomly within the irradiated area. The irradiations were performed using a KX10 therapy unit. Three different X-ray qualities were used with the following characteristics:

(i) 135 kV; 1 mm Al+0.25 mm Cu added filter; effective energy 55 keV
(ii) 105 kV; 0.1 mm Cu added filter; effective energy 38.5 keV
(iii) 30 kV; 0 added filter; effective energy 18.5 keV.

Doses of approximately 1 rad and 5 rad were given for each quality although the corrected doses measured by the ionization chamber instrument were not disclosed to the N.R.P.B. authors until the mean dose estimates for the batches of lithium borate dosimeters had been evaluated by them.

The readings obtained from both systems were corrected for energy response appropriate to the effective energies of the primary X-ray beams. However, at these low energies up to 40% of the dose at the surface of a phantom is due to backscattered radiation which has a lower energy spectrum than the primary X rays. Consequently the correction factors used, which strictly are appropriate only for primary X-ray spectra, may be in error by a few per cent when applied to measurements made at the surface of the phantom.

The dose estimates obtained are compared in Table I. The doses are expressed in rad in soft tissue, appropriate conversion factors (ICRU, 1970) having been used to correct the ionization chamber exposure measurements. The precision obtained in the readouts of the five TL dosimeters, irradiated together and to ostensibly similar doses, is expressed by the standard deviation (σ) and is listed in Table I as a percentage of the mean value.

Agreement between the results obtained with the two systems is remarkably good for 38.5 and 55 keV incident X-ray energies, considering the possible sources of error. At 18.5 keV the readings of the lithium borate are approximately 12% lower than those of the ionization chamber. Apart from the possible errors in the energy correction factors mentioned above, there is also a small error arising from the relatively large size of the ionization chamber and the consequential displacement of phantom material which occurs when the chamber is half immersed in the phantom. Measurements made by Ellis (1976) suggest that for small field sizes and low radiation energies the chamber over-estimates the surface dose rate when operated in the half-immersed position, but no allowance has been made for this effect.

DOSE MEASUREMENTS ON PATIENTS

Sachets of lithium borate powder similar to those used in the phantom measurements were attached to the patients' skin by means of adhesive polythene tape. In general, attempts were made to measure, for complete examinations, the maximum dose to the patients' skin, the dose to the male gonads and the skin dose to the anterior mid-line of female patients at the level of the iliac spines. These latter measurements have been used to estimate an approximate ovarian dose using conversion factors derived by Ellis (Adrian, 1960). The male gonad dose can be measured directly by sachets attached to the inside of the thigh at the level of the testes.

The maximum dose to the patients' skin was measured, in the case of radiography, by means of a single sachet placed on the skin in the centre of the X-ray field. In fluoroscopic examinations, during which the size and position of the X-ray field with respect to the patient were liable to change, an array of several dosimeters arranged in the form of a cross was attached to the patient to cover the area of skin expected to receive the highest dose.

TABLE I

IONIZATION CHAMBER AND LITHIUM BORATE DOSE ESTIMATES ON THE SURFACE OF A MIX D PHANTOM

Effective energy of X-ray spectrum (keV)	Ion chamber dose estimate (rad in tissue)	Lithium borate dose estimate (rad in tissue)	(σ) (%)	Lithium borate dose / Ion chamber dose
18.5	4.90	4.21	2.6	0.859
	0.978	0.878	2.0	0.898
38.5	4.80	4.60	2.3	0.958
	0.969	0.969	1.7	1.00
55	4.99	4.98	2.3	0.998
	0.997	0.995	2.1	0.998

Barium enemas

These examinations were carried out at Hammersmith Hospital using a Siemens Biangulix Rapid undercouch X-ray tube with a Sirecon image-intensifier system. The total fluoroscopic screening time and the number of radiographs taken for each examination studied are shown in Table II together with the relevant patient data and the measured doses. Typical radiological parameters are shown below the table and Kodak RP54 fast film with Siemens Diamate intensifying screens were used for the radiographs which were taken filling the colon first with barium and then with air. The maximum skin dose was measured by means of a cruciform array of dosimeters on the patient's back, centred on the third lumbar vertebrae.

For some of the enemas a Diamentor ionization chamber was available for measuring the product of the exposure and the area of the incident X-ray field at the level of the chamber in units of R.cm^2. By attaching a lithium borate sachet to the centre of the Diamentor chamber to measure the exposure R, the mean area of the X-ray beam in the plane of the ionization chamber was estimated and from this the mean skin irradiation areas for the examination derived. Values for the nine patients investigated are shown in column 8 of Table II. They were useful in estimating the ovarian doses given in the last column of Table II and may be helpful in calculating somatic doses if these should be required.

Intravenous pyelography

The standard routine for intravenous pyelography at Hammersmith Hospital involves an initial full length 17 × 14 in. radiograph and a renal area 12 × 10 in. radiograph prior to injection of the contrast medium, followed by two 12 × 10 in. and two 17 × 14 in. radiographs at specified times after the injection. However, actual examinations rarely follow the standard pattern so variations from this are shown in the last column of Table III which also gives the measured doses and personal data for the 18 patients investigated. The maximum skin dose was measured on the anterior mid-line of the upper abdomen, 5 cm above the lower costal margin, where the full length and the renal area fields overlap.

Cardiac catheterization and angiocardiography

As with barium enemas, the fluoroscopic image during cardiac catheterization at Hammersmith Hospital is viewed on television monitors associated with Sirecon Duplex image intensifiers. Normally the passage of injected contrast medium is observed by cine-fluorography using Ilford Pan F35 mm film at 48 frames per second and occasionally by biplane serial radiography using an Elema biplane film changer. Of the 27 cases investigated, three involved no angiography, one being a cardiac pacemaker implant. Total cine time is shown in Table IV, together with the patients' data and the measured doses. Cases 21 to 27 were small infants, selected so

TABLE II

Data from barium enema examinations

Case no.	Patient data			Total screening time (mins)	No. of films		Mean field area (cm^2)	Max. skin dose (rad)	Dose to testes—measured (rad)	Dose to ovaries—estimated (rad)
	Age	Sex	Size		12 × 10 in.	14 × 14 in.				
1	20	F	small	4.7	4	6		14.1		—
2	60	F	—	4.5	4	4		11.9		0.21
3	50	F	large	11.8	10	6	91	11.2		0.38
4	50	F	average	3.9	3	5	120	9.3		0.33
5	70	F	small	6.3	7	4	104	13.7		0.41
6	50	F	v. large	7.3	6	5	108	22.5		0.19
7	50	M	average	3.3	5	4	118	10.3	0.18	
8	23	F	average	11.5	5	6	81	39.8		0.53
9	61	M	average	7.7	7	3	116	14.2	0.23	
10	52	F	average	5.2	70 mm film (30)		127	18.7		0.25
11	28	M	small	7.3	4	9	156	14.6	0.54	
12	59	F	average	4.9	3	7		11.4		0.29
13	58	M	average	4.8	3	6		17.1	0.13	
14	79	F	small	4.6	5	6		12.4		0.31
15	63	M	average	4.0	7	3		10.2	0.13	
16	28	F	average	3.3	3	6		13.7		0.40

Fluoroscopy: 70–100 kV; 3 mm Al filter; 50 cm FSD
Radiography: 100–115 kV; 10–30 mAs

TABLE III

Data from intravenous pyelography

Case no.	Patient data			Doses (rad)			Comments
	Age	Sex	Size	Upper abdomen	Testes	Ovaries (estimated)	
1	65	F	small	3.83		0.35	
2	30	M	average	6.05	0.135		
3	70	M	average	12.5	0.075		10 films + tomogram
4	63	F	small	1.84		0.067	
5	32	F	average	6.19		0.72	2 extra 12 × 10 in.
6	60	F	average	3.13		0.62	
7	35	F	average	3.66		0.27	2 extra 12 × 10 in + 2 localization
8	31	F	small	2.76		0.43	1 extra 12 × 10 in.
9	58	F	small	2.71		0.16	1 catheter used
10	65	M	average	8.26	0.026		2 extra 12 × 10 in.
11	84	M	small	11.4	0.127		8 films + 5 tomograms
12	42	M	large	5.21	0.068		1 extra 17 × 14 in.
13	26	F	average	3.00		0.15	
14	57	M	small	3.88	1.15		3 tomograms
15	62	M	average	3.73	0.08		
16	51	M	large	17.5	0.56		
17	66	M	average	4.43	0.065		
18	72	M	very small	2.92	1.51		

Radiography: 65 kV; 120 mAs; 102 cm FFD

TABLE IV

Data from cardiac catheterizations and angiocardiography

Case no.	Patient data			* Total screening time (mins)	Total cine time (sec)	Max skin dose (rad)	Dose to testes—measured (mrad)	Dose to ovaries—estimated (mrad)
	Age (yrs.)	Sex	Weight (kg)					
1	29	M	55	27.0	32	44.8	18	
2	11	F	22	17.5	19	15.5		4
3	65	M	85	3.7	0	6.8	30	
4	48	F	70	4.2	0	11.7		∼6
5	9/12	M	9.7	28.0	14	10.9	13	
6	50	M	83	20.0	55	18.1	21	
7	52	M	71	6.2	26	4.25	∼0	
8	50	M	66	11.3	79	10.7	∼5	
9	60	M	64	6.4	67	5.15	∼2	
10	43	F	67	9.0	63	4.0		10
11	42	F	64	10.5	25	30.2		
12	64	M	73	10.7	73	6.85	∼4	
13	4	F	14	—	14	4.9		19
14	3	F	12	28.0	20	11.4		11
15*	71	F	57	10.0	—	11.4		∼3
16	12	F	42	5.0	(biplane)	13.8		∼6
17	61	F	—	6.0	53	6.4		∼4
18	42	M	75	7.2	74	9.9	24	
19	21	F	67	11.5	14	9.9		∼2
20	9	M	27	—	(biplane)	11.7	25	
21	1/12	M	3.1	20.5	7	10.0	70	
22	16/12	F	11	12.3	8	8.9	—	∼5
23	3.5/12	M	4.7	13.5	14	5.4	42	
24	13/12	M	8.6	14.5	7	7.0	26	
25	1/12	M	3.7	14.0	14.3 (biplane)	5.7	32	
26	8/12	M	8.3	16.5	15 (biplane)	9.8	14	
27	3/12	M	5.3	10.8	7	3.6	∼0	

*Pacemaker implant.

Fluoroscopy: 70–100 kV; 3 mm Al filter; 80 cm FSD

Cine: 60–100 kV; 130–320 mA; 80 cm FSD

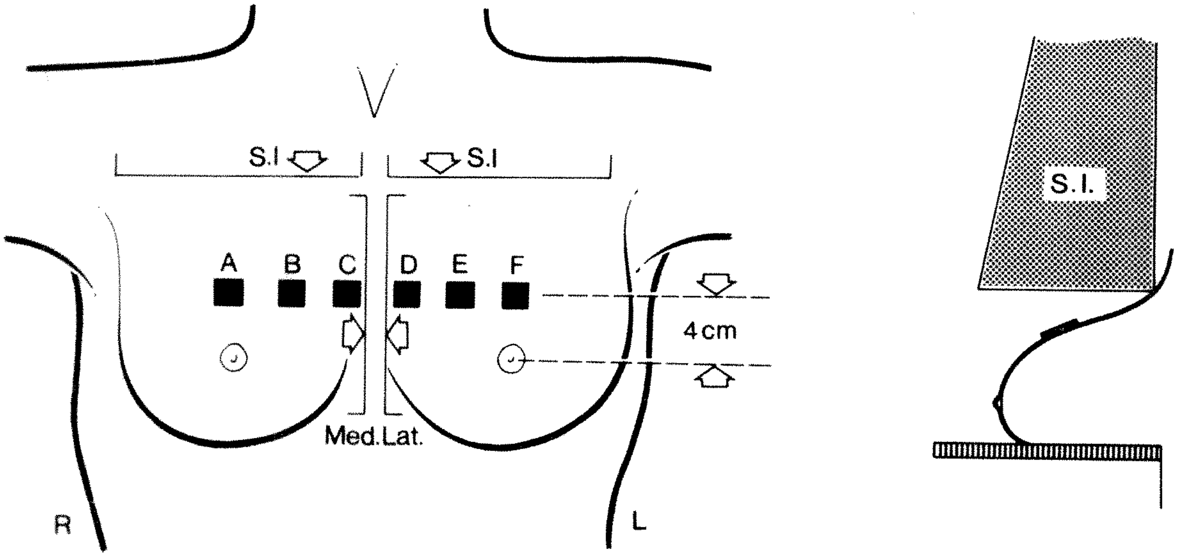

Fig. 1.
Arrangement for TLD sachets for mammography.

that dosimetry measurements based on chromosome aberrations, which require the best approximation to whole body exposure, could be made at the same time (Lloyd *et al.*, 1976).

The maximum skin dose was measured by means of a cruciform array of sachets attached to the patient's back with one arm of the cross lying along the spine and the other at nipple level.

Mammography

These measurements were made at the Royal Surrey Hospital where a two-field technique is usually employed for the examination of each breast, a supero-inferior (SI) field with compression and a medial lateral (ML) field. A Machlett Dynamax Type HD40M rotating molybdenum anode X-ray tube, operated at 30 kV, is used in conjunction with Medichrome blue film with a single-backing calcium tungstate intensifying screen vacuum-packed in a black polythene envelope. The measured half-value layer of the radiation was 7.5 mm Perspex (approx. equivalent to 0.45 mm Al).

Three sachets were attached to each breast in the positions shown in Fig. 1. The doses measured at these positions for 24 patients are shown in Table V, together with subjective classification of breast size in one of six categories ranging from very small (V.S) through medium (M) to large (L). The maximum skin dose in each case is in italic in the Table and values of mAs per film are given for both projections for each patient. Variations from the standard technique are listed in the last column. No attempt was made to measure ovary doses since the X-ray beams give rise to negligible depth dose at the level of the ovaries (Gilbertson *et al.*, 1970; Asbury and Barker, 1975).

Discussion

The measurement of doses by means of lithium borate sachets at a hospital remote from the read-out laboratory has presented few difficulties. The results of the intercomparisons between the ionization chamber kept at Hammersmith Hospital and the TL dosimeters read out at the N.R.P.B. laboratories have demonstrated good agreement between the two systems despite the unavoidable delay of sometimes up to ten days between exposure of the TLD's and read out, and the carriage of the dosimeters by car between Hammersmith and Harwell. Unused dosimeters from measurement sessions at the hospitals have never shown significantly different background values from similar unirradiated dosimeters which have remained at the N.R.P.B. laboratories.

The skin doses measured on patients at the two hospitals appear to be reliable when compared with other data. The expected high values of gonad doses from barium enemas and intravenous pyelograms were confirmed, all being well within the range for which the lithium borate dosimetry system has high accuracy. The gonad doses for the procedures

TABLE V

Data from mammography

Case no.	Age	Breast size	mAs		Doses (rad)						Comments
			SI	ML	A	B	C	D	E	F	
1	—	S	48	40	0.47	—	—	*0.89*	0.44	0.43	
2	—	S/M	48	40	0.38	0.51	0.94	*0.98*	0.48	0.43	
3	—	M	48	40	0.42	0.58	*0.66*	0.53	0.56	0.50	
4	53	M	42	38	1.18	*2.39*	1.05	1.49	2.22	1.89	
5	54	M	42	38	0.62	0.67	0.64	*0.89*	0.85	0.70	
6	42	M	42	38	0.49	0.60	0.68	1.12	*1.24*	0.90	Extra SI film (left)
7	42	L	42	38	0.79	0.84	0.67	*1.07*	0.95	0.72	
8	62	S	42	38	0.65	0.71	0.78	*1.45*	0.96	0.62	
9	39	S	45/60	38	0.62	1.09	1.46	*1.91*	1.87	1.03	Extra SI film (left)
10	16	V.S.	44	29	0.51	0.54	—	0.52	*0.93*	0.53	
11	34	V.S.	39	18	0.33	0.34	0.31	0.25	*0.41*	0.40	
12	24	S/M	42	38/42	1.05	1.34	*1.48*	1.12	0.85	0.73	Extra ML film (right)
13	32	V.S.	44	38/42	0.80	0.81	0.81	0.91	*1.10*	0.89	
14	68	M	38	30	—	—	—	*0.68*	0.58	0.40	Mastectomy (right)
15	45	M	42	38/42	0.96	—	0.80	0.87	*1.01*	0.78	
16	42	M	52	30	0.56	*1.09*	0.68	0.86	1.01	0.61	
17	51	L	52	30	0.48	0.56	0.52	*1.26*	0.82	0.72	Extra ML film (left)
18	31	S/M	52	30	0.30	0.36	0.46	*0.71*	0.68	0.47	SI (right) not measured
19	42	M	46	30	0.42	0.56	0.52	*0.75*	0.64	0.52	
20	47	M/L	52	38	0.65	0.69	0.79	*1.12*	0.90	0.68	
21	43	S	46	24	0.39	0.46	0.42	0.57	*0.63*	0.43	
22	26	M	52	29	0.58	*1.35*	0.94	0.87	0.69	0.52	
23	49	M	46	24/28	0.49	0.56	0.53	*0.64*	0.55	0.45	
24	49	S	40	20	0.35	0.36	0.37	*0.50*	0.44	0.32	

Breast size: V.S. = very small; S = small; M = medium; L = large.
Radiography: 30 kV; 0.6 mm Al inherent filtration; 70 cm FFD

involving cardiac catheterization were understandably much smaller involving some loss of accuracy in the measurement of doses much below 10 mrad (Langmead and Wall, 1976). However, analysis of the dose data from the Adrian survey (Adrian, 1960) shows that the contribution of gonad doses below 10 mrad to the genetically significant dose (GSD) from diagnostic radiology in the U.K. was less than 2%. Consequently the reduced accuracy of the measurement of doses below 10 mrad made with lithium borate dosimeters will not result in significant errors in the estimation of the GSD.

The skin doses measured during cardiac catheterization were high, chiefly due to the long fluoroscopic screening times involved. Comparison with skin doses estimated for similar examinations on 89 patients at the Brompton Hospital in 1967 (Gough, *et al.*, 1968) indicate that some improvement has been achieved with the present diagnostic techniques since the mean value of maximum skin dose per adult examination in the present series is 13 rad compared with 39 rad in the Brompton Hospital series. This difference is statistically significant for the distributions of doses obtained at the two hospitals, despite the wide range of values encountered (typically the standard deviation is about 75% of the mean). However, an accurate measure of the degree of improvement that has been achieved is not possible since the method used for determining the skin doses at the Brompton Hospital was different from the one used at Hammersmith and is therefore likely to involve different systematic errors. The sample of 17 adults measured at Hammersmith is probably too small to give a representative distribution of the different types of examination that are included under the general title of cardiac catheterization and angiocardiography.

The doses to breasts measured during mammography at the Royal Surrey Hospital were encouragingly low and in good agreement with recent results obtained by other authors investigating the same diagnostic technique (Young, 1974; Asbury and Barker, 1975; Stillman and Palmer, 1975). The mean value of the maximum surface doses measured for complete four field examinations at the Royal Surrey Hospital was 1.05 rad and the maximum value recorded was only 2.39 rad. These are very close to the values obtained for the same parameters at the South Manchester Breast Clinic by Asbury and Barker and agree well with the estimate of 0.54 rad per single film made by Young for the same mammography technique at the Edinburgh Royal Infirmary.

A similar series of measurements comparing Medichrome Blue Films with conventional black-and-white film for mammography was carried out by one of the authors (K.P.) at Hammersmith Hospital and is reported elsewhere (Stillman and Palmer, 1975). The mean dose, measured at a position corresponding to D in Fig. 1 of this report, for 19 patients investigated with the same technique as used at the Royal Surrey Hospital, was 1.47 rad and the maximum value of the dose at D was 2.9 rad. This is in good agreement with the present data taking into account the higher proportion of large breasts in the Hammersmith series.

Although the dose received by the patient when undergoing mammography at the Royal Surrey Hospital has been shown to be satisfactorily low, it should be emphasized that no attempt has been made in this work to assess the adequacy of the image quality obtained using the Medichrome Blue and single calcium tungstate film-screen combination. However, it has been shown elsewhere (Ardran *et al.*, 1975) that even lower doses may be achieved with comparable image quality using a similar radiological technique but in conjunction with one of the recently introduced Trimax film-screen combinations.

Conclusions

The lithium borate powder dosimetry system, chosen for its suitability for the operational measurement of doses to patients undergoing radiological procedures, has proved to be entirely satisfactory for this purpose. The small dosimeter sachets, approximately 1 cm square, are easily attached to the patient's skin using adhesive polythene tape, causing minimal discomfort to the patient and little inconvenience to the radiologist. Unlike ionization chambers and even lithium fluoride dosimeters, lithium borate sachets are invisible on radiographs (even on mammograms) and hence introduce no interference with diagnosis.

The experience gained and the doses measured will provide a valuable guide in planning more extensive surveys at other hospitals as a contribution towards a reassessment of the population dose from medical X rays in the United Kingdom.

Acknowledgements

We should like to express our thanks to Professor Steiner and his staff for their co-operation in allowing us to make measurements on their patients, and our gratitude also to Miss D. Merry, H.D.S.R. and Miss P. Kearnie, D.S.R. and others of the Angiography Unit for their cheerful assistance.

Thanks are also due to Mr. P. D. Butler, M.S.R., for facilitating the dose measurements on patients undergoing mammography at the Royal Surrey Hospital, Guildford.

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Technical note

The Edinburgh afterloading technique for carcinoma of the uterine cervix

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A partially afterloaded line source system was developed in Edinburgh and put into use in 1960 (Campbell and Douglas, 1966). In this system the intra-uterine source was preloaded and only the vaginal component afterloaded. With the availability of small caesium sources a modification has been made to allow full but manual afterloading. The sources manufactured by the Radiochemical Centre at Amersham, are 5 mm in length and 2 mm in diameter. The treatment régime is very similar to that described by Campbell and Douglas (1966).

DESIGN OF THE CAESIUM APPLICATORS

A new flexible intra-uterine applicator has replaced the straight tube used in the earlier system, and the construction of the complete applicator is shown in Fig. 1. The external appearance of the vaginal applicator has not changed and still consists of Perspex bobbins and a perineal bar threaded over a stainless steel tube. Lead shielding is used posteriorly, and the applicators are available from 2 cm to 4 cm in diameter. The length of the intravaginal portion can be varied by altering the position of the perineal bar, and a screw locking nut at the lower end keeps the component parts firmly in place. The main difference between the present applicator and the previous one is that the central steel tube is not sealed at the proximal end. This allows the extrusion of a flexible Portex tube into the uterus after passage through the central steel tube of the vaginal applicator. This Portex tube (shown again in Fig. 2B) ultimately accommodates the caesium source holder (Fig. 2C), and is 4 mm in diameter and of varying length corresponding to the source holder. A small metal collar denotes the level of the external os, and is therefore the lower limit of the intra-uterine sources. The vaginal applicator (Fig. 2D) can slide over the Portex tube as far as this metal collar.

The intra-uterine source holder is made of flexible steel mesh 2.5 mm external diameter and is available in varying lengths to accommodate a uterine cavity 3, 5, 6, 7 or 9 cm long. This holder is sealed at both ends and screws into the vaginal source holder (Fig. 2C) and therefore complete interchangeability of both applicators is possible. The caesium loading is uniform and varies from 20 to 70 mg radium equivalent according to the length of the holder (from two to 11 individual sources). The vaginal portion of the source holder is a rigid steel tube again 2.5 mm in diameter, and may contain from 25 to 70 mg radium equivalent (two to six sources). Loading is again

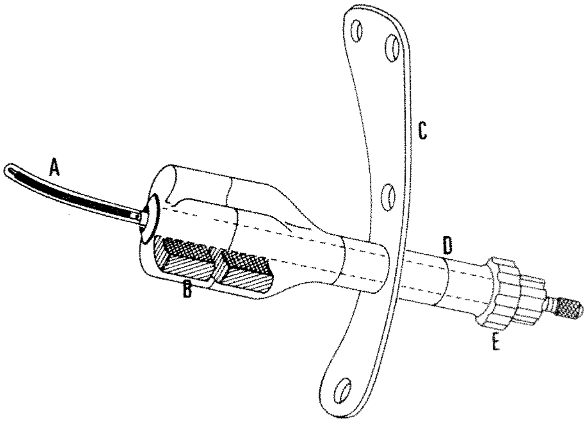

FIG. 1.
The Complete Applicator
A—Intra-uterine applicator
B—Lead Shielding
C—Perineal bar
D—Perspex bobbins
E—Locking nut

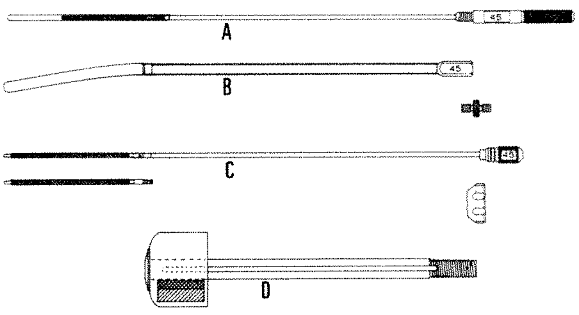

FIG. 2.
A—Introducer
B—Source holder, Portex tube attached to stainless steel tube
C—Intra-uterine and vaginal source train
D—Central steel tube of the vaginal applicator

uniform except in the 70 mg holder where the source strength is slightly reduced at the end of the source train. The lower end of the holder has a screw thread and also bears a figure denoting the mg radium equivalent of the caesium.

In order to obtain the correct overall length of the source trains, spacers are inserted between the active sources. These spacers are 2 mm long in the intra-uterine holder and 4 mm long in the vaginal holder. A dummy source holder is initially inserted until a radiological check has verified the correct position of the applicator.

METHOD OF INSERTION OF THE APPLICATOR

Silver seeds are inserted into the cervix as radiological markers at a preliminary staging examination carried out under anaesthesia. In the assembly of the applicator, it is usual to place two Perspex bobbins containing lead protection posteriorly at the upper end, but this may be altered according to the length of the vagina or the extension of the tumour down the vagina. In an unusually narrow vagina, smaller diameter bobbins 2.5 or 3 cm in diameter are used without lead protection.

The cervix is then dilated to No. 6, and the utero-cervical canal is measured. A source holder of suitable length is chosen and inserted into the uterus. The steel collar at the lower end of the intra-uterine portion should be visible at the os. A catheter must be inserted into the bladder at this time through the aperture in the perineal bar. The applicator is then threaded over the Portex source holder until the lower metal tab of the introducer (Fig. 2A) projects through the lower end of the steel rod. The introducer is then removed. A double-threaded locking nut is now screwed into the lower end of the source holder, thus completing assembly.

It only remains to pack carbonet and gauze around the vulva. It is important to keep the perineal bar in close opposition with the vulva during this operation. Tapes are then passed from the back of an abdominal belt through the posterior and anterior holes of the perineal bar and secured to the front of the belt. This method has proved to be extremely simple in use and the position of the caesium is virtually guaranteed.

DOSAGE MEASUREMENT AND CALCULATION

The dose distribution around individual caesium sources was measured in a water bath by two independent methods:

(1) a PTW micro-ionization chamber, and
(2) a needle geiger tube.

Both methods showed that the exposure rate obeyed inverse square law at distances between 1.5 cm and 10 cm from the source and the error introduced by an assumption of spherical isodoses around the source was small enough to be ignored.

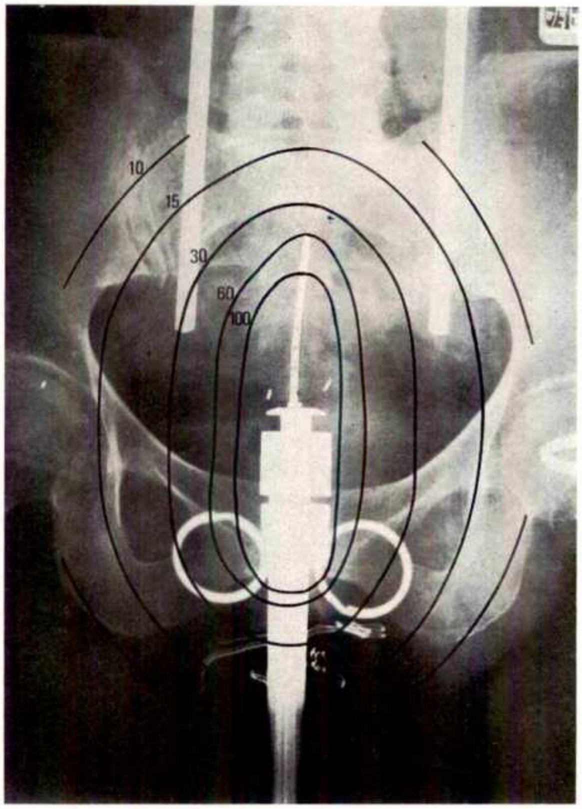

FIG. 3.
Antero-posterior radiograph (dose rates in rad/hr)

Absolute measurement of the absorbed dose rate around an individual source was obtained by the use of lithium fluoride. Uniform exposure of the entire sample was obtained by correct positioning, and dose values were calculated by comparison with standards irradiated to a known dose on a 4 MV linear accelerator. This procedure was carried out for a number of sources, and the results when used in conjunction with the Amersham test reports gave an effective value for the K-factor. An estimation was also made of the attenuation in the steel walls of the vaginal applicator at the point where the dose to the patient would be specified. These results compared satisfactorily with those calculated by summation of the contribution from each individual source. Figure 3 is an antero-posterior radiograph of a dummy source holder in position within a patient, and also shows the dose distribution obtained for that particular insertion.

TABLE I

Average yearly exposures in mR in the year preceding and following the introduction of the fully after-loaded system

	1971	1973
Theatre Staff	770	100
Radiotherapist	360	40
Diagnostic Radiographer	800	60
Senior Ward Nursing Staff	470	250

Radiation Protection Results

The full afterloading system was introduced in 1972, and Table I shows the average yearly exposure in mR for the year preceding and the year following this introduction for the staff most closely concerned with the technique. Approximately 200 insertions a year were performed. As shown, a very significant reduction in dose to the staff has been achieved.

A lead screen also provides radiation protection around the patient's pelvis during the time of the caesium insertion, and as expected the reduction in exposure to ward nursing staff is not so marked.

Acknowledgment

We wish to thank other members of the Medical Physics Department, both past and present, who have collaborated in the development and production of this system.

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Book review

Natural Background Radiation in the United States. N.C.R.P. Report No. 45, pp. xi+163, 1975 (Washington, N.C.R.P. Publications).

This report runs to some 130 pages and contains 57 tables of data. In compiling it, the authors have drawn on vast quantities of recorded measurements and have included extensive calculations and estimates.

Cosmic radiation, cosmic ray produced radioactivity, terrestial radionuclides and the effects of radionuclides both in the soil and in the air are all dealt with. A considerable amount of space is devoted to the calculation of dose levels received by man. Although many of the data relate directly to measurements made in the United States and to dose calculations in that country, much of the report deals with the subject on a global basis. In an appendix, data are presented on the fall-out from nuclear tests together with calculations on human body dose and dose commitments resulting from the tests.

One section deals with measurements of cosmic radiation and associated absorbed dose rates, and gives the results of observations made in the upper atmosphere extending to heights of 25 kilometres above ground level. Following from this, estimates are given of the dose rates to which aircraft passengers are exposed.

The summary of the report contains a table giving average values of dose equivalent rates from various sources of natural background radiation, under the headings gonads, lung, bone and G.I. tract.

It is an excellent report.

N. W. Ramsey.

1976, *British Journal of Radiology*, *49*, 966–967

Case reports

Angiographic demonstration of gastrointestinal bleeding due to aorto-duodenal fistula

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(*Received October, 1975*)

Aorto-enteric fistula is an uncommon complication of abdominal aortic aneurism and a rare cause of gastrointestinal bleeding.

Awareness of this entity and careful timing of arteriography may, as illustrated in this case, lead to a definitive pre-operative diagnosis.

Review of the literature reveals that this is the first report of an aorto-duodenal fistula demonstrated angiographically.

Case Report

A 59-year-old female was admitted with a history of two episodes of transient malaena, the first occurring one week before and the second one day before admission. There was no history of haematemesis, abdominal or back pain. She had ischaemic heart disease, familial hyperlipidaemia, and was on replacement therapy for hypothyroidism which had developed as a result of I^{131} therapy for non-toxic goitre.

On physical examination she was obese and had a vaguely palpable epigastric mass. Haemoglobin was 7 g%, blood pressure 150/70, and pulse rate 100 per minute. The plain abdominal radiographs, barium meal and enema, endoscopy and sigmoidoscopy were normal. She had several further brief episodes of malaena while in hospital and arteriography was planned when she next showed signs of haemorrhage.

On the 25th day after her initial rectal bleed, a selective superior mesenteric arteriogram was performed to outline the source of bleeding. This demonstrated considerable reflux of contrast agent into the abdominal aorta, outlining an aneurysm 5 cm in diameter, and a relatively dense blush appearing in the region of the third and fourth parts of the duodenal loop with spread into the second portion (Fig. 1).

The aortogram showed the saccular aneurysm arising below the renal arteries (Fig. 2). The patient was immediately transferred to the operating theatre, where the arteriographic findings were confirmed. A laminated clot-filled saccular aneurysm was found intimately adherent to the third part of the duodenum and the left renal vein. There was fistulous communication, 3 mm in diameter, between the aneurysm and the third part of the duodenum. At the time of operation, the entire large and small bowel were empty of blood and there was no bleeding from the fistula.

The aneurysm and distal atheromatous aorta were resected and replaced by a Teflon prosthesis, and the duodenal fistula closed. The patient died 24 hours post-operatively from disseminated intravascular coagulation. Histology of the resected specimen showed atherosclerotic changes associated with low-grade inflammation and fibrosis at the site of the fistula.

Discussion

Arteriography has an established place in the investigation of gastrointestinal bleeding (Baum, 1971) and the presence of an abdominal aortic aneurysm should not be regarded as a contra-

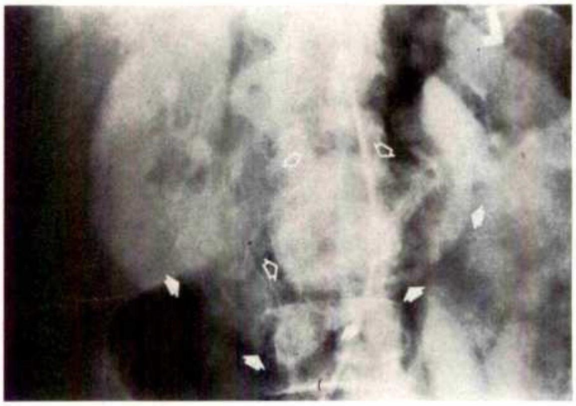

Fig. 1.

Eight-second radiograph shows the duodenal loop from the second part to the ligament of Treitz (white arrows). The aneurysmal sac is seen at its superior margin (clear arrows).

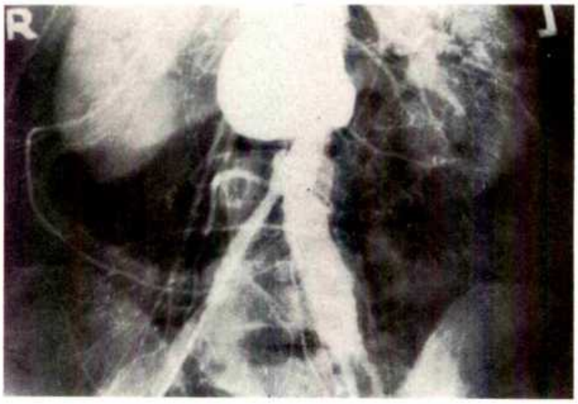

Fig. 2.

Abdominal aortogram demonstrates the saccular aneurysm and atheromatous changes.

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indication to arteriography (Rogoff and Lipchik, 1971; Brewster *et al.*, 1975; Robiscek *et al.*, 1971; Kahn and Callow, 1966).

It is generally accepted that bleeding due to aorto-enteric fistula is massive and fatal within a few hours (Macbeth, 1962; Hirst and Affeldt, 1951). In fact, it is rarely exsanguinating in the first episode, and quiescent periods without bleeding may vary from days to months (Law *et al.*, 1962; Ozlu and Allen, 1961; Schramek, *et al.*, 1971; Lawaetz, 1972; Dinapoli *et al.*, 1962).

The triad of abdominal pain, abdominal mass and gastrointestinal haemorrhage should suggest the diagnosis of aorto-enteric fistula, but this triad is infrequent (Furguson and Arden, 1966). Of the 129 cases of aorto-enteric fistula analysed by Reckless *et al.*, (1972), aneurysms were palpable in only 55%.

The most common causes of primary aorto-enteric fistula are arteriosclerosis (61%), syphilis and tuberculosis (each 8%) and mycotic aneurysms (Reckless *et al.*, 1972). Since 1951 several cases have been reported following prosthetic replacement of an aortic aneurysm (Oor and Ware, 1968), By far the most common site for fistula formation is the duodenum.

ACKNOWLEDGEMENT

We wish to thank the superintendent of Groote Schuur Hospital for permission to publish this case.

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Enteric duplication with fistulation into the aorta

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(Received May 1976)

Ulceration and fistulation are recognized complications of enteric duplication (Bockus, 1963). Bleeding may be a prominent feature (Tabrinsky *et al.*, 1973). We would like to report a case in which a fistulous connexion between a duplication and the aorta was encountered and in which arteriography proved hazardous.

CASE HISTORY

The patient, an eight-year-old boy, originally presented shortly after birth with a mass in the left upper quadrant of the abdomen. Laparotomy 18 months later revealed a large retro-gastric cyst, which was anastomosed to the posterior wall of the stomach. A heart murmur was discovered at this time and later a diagnosis of aortic stenosis was made. At about this time he was found to have iron deficiency anaemia. Occult blood was present in the faeces, and oral iron was given at intervals, with a good response. His spleen was enlarged.

Other abnormalities found subsequently included an unusual square habitus and large head, retarded bone age, a Klippel-Feil deformity of the cervical spine and abnormal lung function tests. He occasionally complained of epigastric pain.

The present admission to hospital resulted from severe anaemia (the lowest recording during this admission was 3.4 G/dl). He was transfused. Melaena stools were noted and

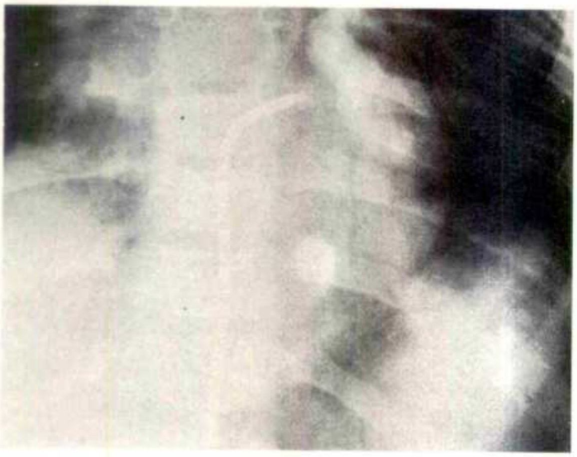

Fig. 1.

Contrast in a space to the left of the spine. The catheter has been advanced above this.

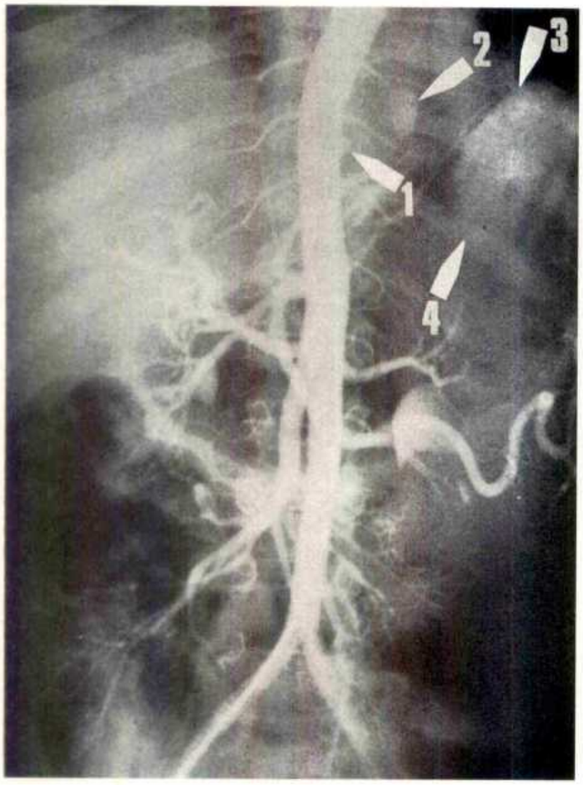

Fig. 2.

Free aortic injection. The aorta appears to curve. A small diverticulum (1) fills with contrast. The pool of contrast shown in Fig. 1 is still present (2). Contrast is present in gastric fundus (3, 4).

vomiting on some occasions contained blood. Barium studies gastroscopy and sigmoidoscopy were all normal.

At laparotomy blood was present in bowel above and below a Meckels' diverticulum. This was removed. No ulceration was present in it and no other obvious source of bleeding was found. Further melaena stools followed and arteriography was requested.

Procedure

The aorta was catheterized via the right femoral artery using a short curve ended catheter with one side hole.

The catheter was advanced under visual control. In the low thoracic region the curved end moved abruptly to the left. Injection of 2 to 3 mls of contrast revealed a small cavity to the left of the aorta (Fig. 1) and a small jet of contrast could be seen passing to the left. The catheter was immediately removed to a higher position in the aorta and a free injection of contrast made (Fig. 2). No abnormal passage of contrast other than into a small projection from the left of the aorta was seen. The catheter was reintroduced into the cavity and a hand injection of some 5 mls of contrast outlined a hollow structure (Fig. 3). It was then evident that severe internal haemorrhage was in progress. Immediate transfusion was followed by laparotomy. During this fatal cardiac arrest occurred.

Post Mortom Examination

An alimentary duplication lined by gastric mucosa with a rugal pattern was present.

It extended from the level of the lower oesophagus where it measured 3.5 × 1.5 cms and expanded into a retrogastric sac measuring 8 × 6 cms. The original surgical communication measured 0.2 cms. In the upper paraoesophageal part of the sac an area of ulceration of 1 cm diameter was eroding

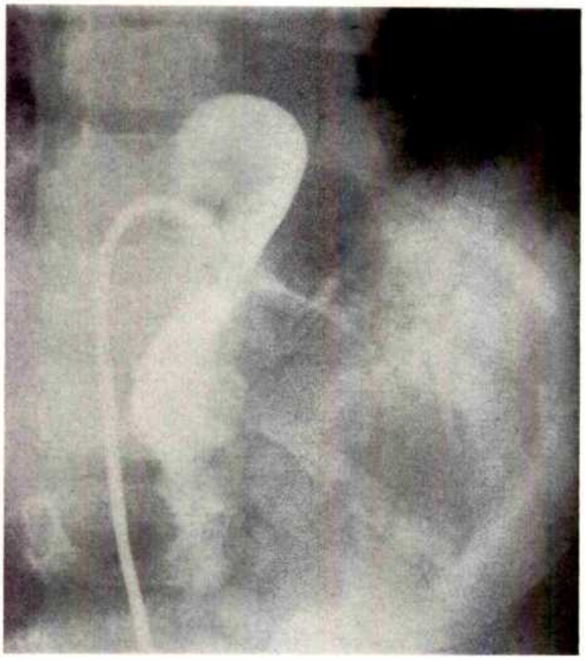

Fig. 3.

A second injection reveals a large cystic space.

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a small vestibule that communicated with the aorta through a 0.5 cms diameter hole in the left anterior aortic wall. Congenital aortic valve stenosis was present.

DISCUSSION

The source of severe gastro-intestinal bleeding may be shown by arteriography.

As this patient had a number of congenital abnormalities, it seemed possible that a vascular malformation might be present in the gut. Although severe haemorrhage was clearly provoked by catheterization, it seems likely that profound and probably fatal spontaneous bleeding would not have been long delayed. We have been unable to find a report of any similar case.

ACKNOWLEDGMENTS

We are indebted to Mr. B. L. Dowling and Dr. J. V. Clark for operative and post-mortem information. Also to Mr. G. B. Dun and the Department of Medical Illustration of Northampton General Hospital.

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Epiploic lipomatosis and lipomatous polyposis of the colon

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(*Received March, 1976*)

Epiploic lipomatosis is a rare condition characterized by massive hypertrophy of the appendices epiploicae of the colon. It is thought to represent a hamartomatous proliferation of the fatty colonic tags and presents early in childhood, with abdominal pain, distension and diarrhoea. The case we wish to report had, in addition to the fatty intra-abdominal tumours, multiple lipomatous polyps in the colon and multiple subcutaneous lipomata. This case is of interest, not only because of its rarity but because it also demonstrates both regression and growth of the various lipomata during the 13 years of follow-up. This is a recognized feature of the hamartomatous type of neoplasm (Morson, personal communication).

CASE REPORT

The patient, presented at the age of nine months when his mother noticed a protruding abdomen and intermittent diarrhoea. He was thought to have coeliac disease but a gluten-free diet had no effect on his symptoms. In 1964, at the age of four, he was again seen because of abdominal swelling and his mother had also noted swellings on his scalp, right axilla and back. Clinically, at this stage, he was found to have a soft abdominal mass with a "doughy" feel and further masses of fatty consistency on the scalp, axilla and back. Biochemical, haematological and stool analyses were normal, as was the jejunal biopsy. A plain abdominal radiograph (Fig. 1) showed a large, lobulated soft tissue mass in the left side of the abdomen, displacing bowel upwards and to the right. This was thought to represent a bowel duplication and laparotomy was performed. At surgery, there were massive deposits of fat in the taeniae of the whole colon. The omentum was not affected and histological examination of the masses showed them to contain only fat. The clinical features of the case were reported by Swain *et al.* (1969).

A subsequent barium meal and follow-through examination, apart from showing displacement of the small bowel, was normal. A barium enema (Fig. 2) showed multpile 1–2 mm smooth polyps extending from the ano-rectal junction to the distal part of the descending colon. Sigmoidoscopy and biopsy of one of the polyps showed deposits of fatty tissue in the mucosa and submucosa of the bowel.

We have recently seen this patient for re-assessment. He is now 15 years of age and of average size and weight. He is asymptomatic. On examination, there are no palpable abdominal masses and the subcutaneous lipomas on his scalp, axilla and trunk have disappeared. Sigmoidoscopy showed

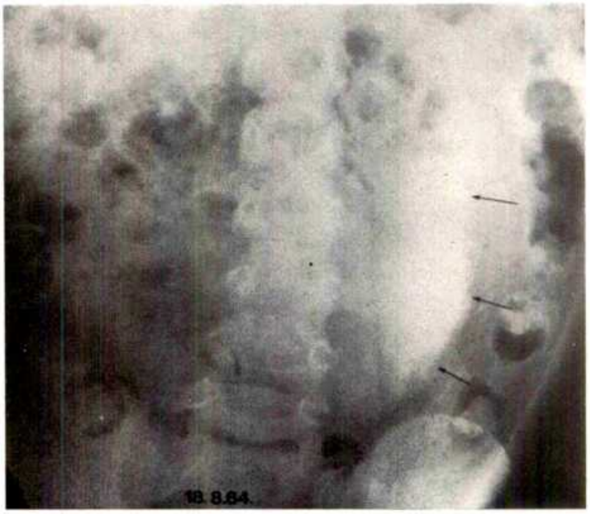

FIG. 1.

The lobulated soft tissue mass (arrows) is displacing the small bowel.

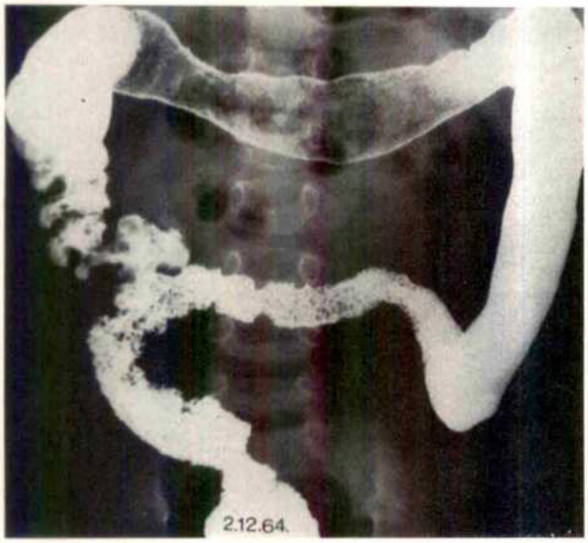

FIG. 2.

There are multiple small polyps in the sigmoid colon and rectum.

multiple small polyps which were easily indented with a probe. A double-contrast barium enema (Fig. 3) again showed multiple small polyps in the same distribution as was noted ten years previously. However, there are now three larger 2 cm polyps in the sigmoid colon. Colonoscopy showed that the polyps extended up to the mid-descending colon and biopsies showed changes similar to those noted previously. Routine haematological and biochemical screening was normal and there was no abnormality of the serum cholesterol, lipo-proteins or immunoglobulins.

DISCUSSION

Hamartomatous types of polyps are very rare and include the lipomatous variety (Bussey, 1970). This case represents one of these varieties, with associated massive hypertrophy of the appendices epiplocae, of the colon and skin lipomas. The one previously reported case (Godenne *et al.*, 1957) had similar enlargement of the appendices epiploicae but had no colonic polyps and no evidence of skin lipomas. The masses of colonic fat in both cases were on the anti-mesenteric side of the colon. In this case, the fatty deposits presented as an abdominal mass of normal soft tissue density on the plain abdominal radiograph and this mass caused displacement of the normal bowel gas shadows. The double-contrast enema showed the multiple small polyps with enlargement of three of these. These larger polyps measured from 2 to 2.5 cms.

In view of the unpredictable natural history of hamartomas and because of the spontaneous remission of the epiploic masses and of the skin lipomata, it is possible that the colonic polyps will remit also. Spontaneous disappearance of the larger colonic lipomas is also possible as this is a not uncommon phenomenon with single lipomatous polyps. It is probable that this patient has a good prognosis, when one considers that the case reported by Godenne *et al.* was alive and asymptomatic eight years after the initial diagnosis.

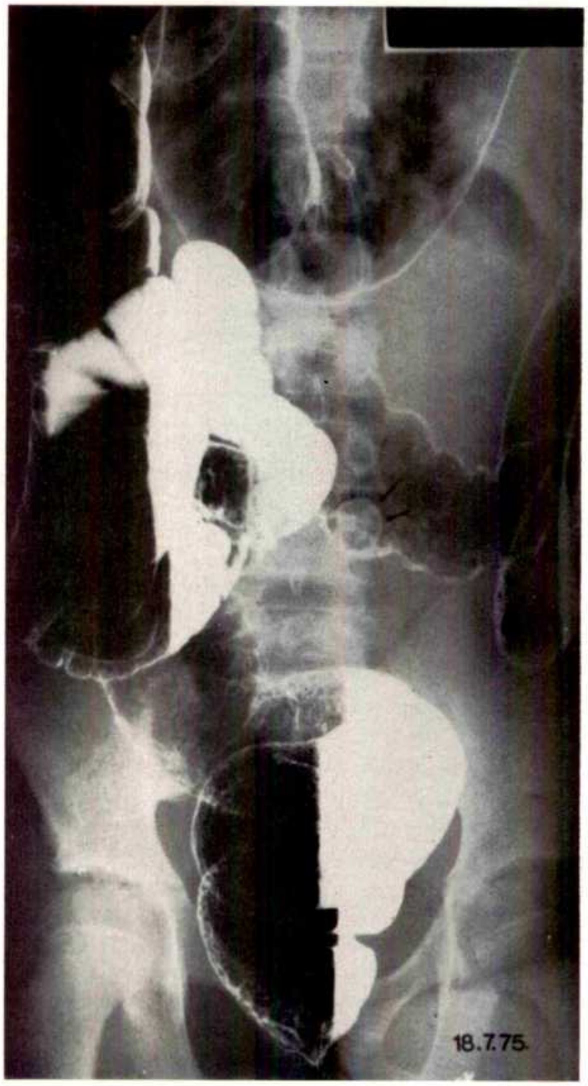

FIG. 3.

Note the multiple polyps in the distal colon and rectum. One of the three larger polyps is arrowed.

The differential diagnosis of multiple colonic polyposis in childhood includes familial polyposis, Peutz-Jeghers syndrome, Gardners syndrome, Cronkite-Canada syndrome, intestinal ganglioneuromatosis, and Turcot syndrome. Lymphoid

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hyperplasia of the colon also causes multpile small polypoid masses, 1 to 4 mm in diameter, but the polyps usually have a characteristic central umbilication (Capitanio and Kirkpatrick, 1970).

Although the case described here represents a rare syndrome which has not been previously deescribed in the radiological literature, it ought to enter the differential diagnosis of multiple colonic polyposis in childhood, especially if there is an associated abdominal mass or cutaneous lipomata.

ACKNOWLEDGMENTS

We are very grateful to Dr. Basil Morson and Dr. Norman France for the histological examinations. We wish to also thank Dr. Christopher Williams, who performed the colonoscopy.

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Primary intrasellar germinoma*

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(*Received May, 1976*)

The purpose of this communication is to report a primary intrasellar germinoma, causing expansion of the pituitary fossa and outlined by air in the suprasellar cistern.

The term suprasellar germinoma is now generally used in preference to ectopic pinealoma, atypical teratoma or a teratoid, to describe a rare malignant tumour which is histologically identical to testicular seminoma and ovarian dysgerminoma. Various authors seem to agree that the tumour probably arises from ectopic germ cells that have been misplaced during their migration from the yolk sac to the gonads in embryogenesis (Simson *et al.*, 1968). These tumours occur more frequently in males, 10 to 30 years of age and reach a peak incidence in the later half of the second decade (Rubinstein, 1972). The majority of intracranial germinomas arise in the pineal region and only few may be found above the pituitary gland. These have been classified according to their relation to the hypothalamus into three types (Kageyama and Belsky, 1961). In the first type, the hypothalamic lesion occurs in association with a similar tumour in the pineal region. In the second and third types, there is a single lesion arising in the floor of the third ventricle or beneath the cerebral hemispheres in the region of the optic chiasm. In the later stages of the disease, these two types cannot be differentiated and extension into the hypophyseal fossa may occur. Under these circumstances, the suprasellar cistern is invariably obliterated. To our knowledge no case has yet been reported where the tumour was shown at pneumoencephalography to arise primarily within the pituitary fossa.

CASE REPORT

A 15-year-old boy was investigated for intermittent frontal and retro-orbital headache of six weeks duration. For the last two weeks prior to admission, these attacks became more frequent and severe and were accompanied by blurring of vision, occasional diplopia and a droop of the left eyelid. His appetite had diminished and he had been feeling tired.

On examination, the patient was a tall, slender adolescent. The optic fundi were normal. A bitemporal hemianopia was defined, with the field defect more dense and extensive on the left side. Slight ptosis of the left eyelid was noted, but external ocular movements were normal. Endocrine assessment documented definite deficiency of anterior pituitary function. Diabetes insipidus was not apparent clinically, but was revealed by a profuse diuresis in response to pre-operative administration of corticosteroids.

The skull radiographs showed uniform expansion of the pituitary fossa with erosion of the lamina dura of the floor of the sella and the anterior wall of the dorsum sellae. A computerized transverse axial scan (Ct) showed small tumour extension into the suprasellar cistern. This was better defined at pneumoencephalography, where a large portion of the tumour circumference was outlined by air in the sagittal and coronal projections (Fig. 1).

At operation, by the trans-sphenoidol approach, the floor of the sella was found to be substantially destroyed and a firm, greyish-red tumour bulged into the sphenoid sinus. The tumour was incompletely excised from the sella.

Histological examination of tumour biopsy showed the characteristic features of germinoma (Fig. 2). Post-operative radiotherapy was given to the primary site, the cranium and the spine.

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*Requests for reprints to Dr. M. J. Malot.

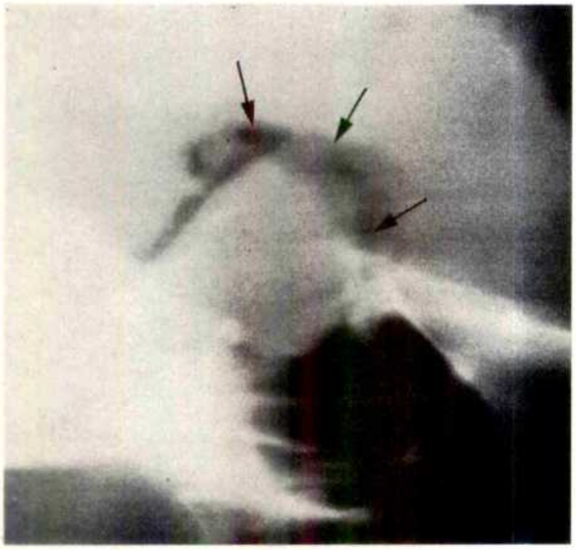

FIG. 1A.

Pneumoencephalotomogram of the sellar area in the lateral projection depicting: (1) almost complete destruction of the floor of the sella, (2) thinning of the dorsum sellae, (3) air outlining the suprasellar extension of the tumour (arrows). Note that there are two thick bands of tumour tissue extending into the hypothalamus.

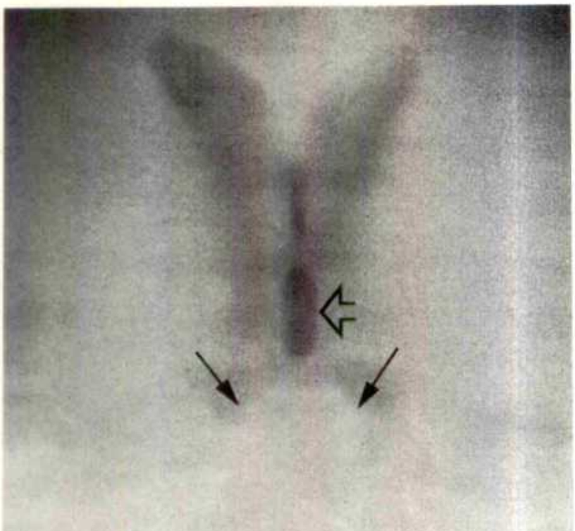

FIG. 1B.

Antero-posterior view of the same tumour outlined by air in the suprasellar cistern (solid arrows). Open arrow points to the third ventricle.

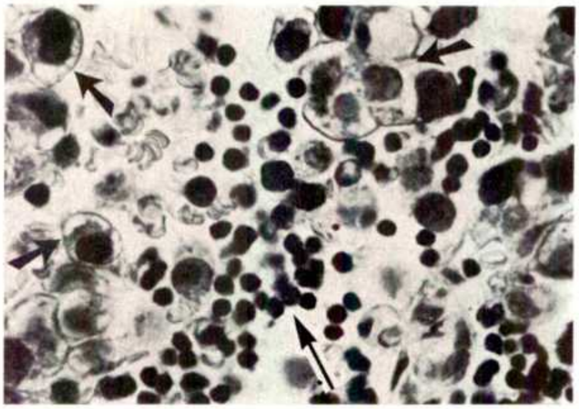

FIG. 2.

Microscopic section H. & E. × 128 showing typical appearances of germinoma. Two distinct types of cell are present: (1) large spheroidal cells with central nuclei (thick arrows) and (2) lymphocytes (thin arrow).

DISCUSSION

Germinoma arising in the region of the hypothalamus is an exceedingly rare tumour that usually remains localized to the suprasellar area. Only in advanced cases does the tumour extend into the hypophyseal fossa and invade the pituitary gland. Clinically, a characteristic triad of diabetes insipidus, visual failure and varying degrees of hypopituitarism is usually present (Kageyama and Belsky, 1961). Many authors have emphasized that diabetes insipidus is the most common presentation and may be the only symptom for many years (Rubin and Kramer, 1965; Kageyama, 1971). This feature may help to differentiate between germinoma and tumours such as craniopharyngioma in which diabetes insipidus is often seen post-operatively.

Radiologically, tumour calcification is rare in suprasellar germinomas and only few cases are associated with an abnormal pituitary fossa (Ghatak *et al.*, 1969). Rubin and Kramer (1965) estimated that sellar changes are present in 20% of the cases. The case here presented is to our knowledge the first of its type in which a germinoma was shown to arise primarily within the pituitary fossa, causing uniform expansion and erosion of the sella turcica. At pneumoencephalography, the tumour circumference was outlined by air in the suprasellar cistern. This is unlike most of the cases in the literature where a filling defect in the third ventricle, with obliteration of the cistern has been described. Initially, our case was thought to be a chromophobe adenoma, but our attention was drawn to the possibility of germinoma following profuse diuresis in response to pre-operative administration of corticosteroids. According to Kageyama (1971), diabetes insipidus is induced when the neurohypophysis and hypothalamus are affected without interruption of the function of the adenohypophysis. Symptoms of diabetes insipidus may begin to disappear if the function of the adenohypophysis is involved. Similarly, if the function of the adenohypophysis and neurohypophysis are affected from the beginning, diabetes insipidus may not be apparent clinically, but even in such a case, it is unveiled upon administration of steroids.

In the present case, we assume that the tumour had invaded the anterior pituitary and then spread upwards to the hypothalamus. This would explain the absence of diabetes insipidus until steroids were given. That the suprasellar cistern was outlined by air at pneumoencephalography would not rule out microscopic invasion of the hypothalamus. In fact, retrospectively, one can detect a few thick bands of tumour tissue extending across the cistern into the hypothalamus.

The CT scan, because of the small size of the lesion, was not helpful. With larger tumours however, the scan may reveal the invasive nature of the lesion. A germinoma, in common with many other neoplasms, may increase its density following the intravenous injection of contrast media (Scully *et al.*, 1975).

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1976, *British Journal of Radiology*, 49, 974

Short communication

Neutron beams generated by protons on beryllium

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(*Received June, 1976*)

On May 7 and 8, 1976, we made preliminary measurements to determine certain physical properties of neutron beams produced by protons incident upon lithium and beryllium targets.* Measurements were made using the 76-inch isochronous cyclotron at the University of California, Davis, at proton energies of 26 MeV, 35 MeV, and 45 MeV. A benelex† (pressed wood) collimator, 66 cm long, was employed to define a 10 cm × 10 cm field at 125 cm from the target. The complete results of these measurements will be reported in a forthcoming paper. We believe, however, that the 26 MeV data may be of immediate interest as several cyclotrons capable of producing protons of this energy are in operation.

The tissue kerma rate in air of neutrons plus gamma rays at 125 cm from the target was measured with a tissue-equivalent ionization chamber filled with tissue-equivalent gas. For 26 MeV protons incident upon a thick (1.27 cm) beryllium target, we obtained 0.47 rad/minute/microampere of beam current. Depth dose was measured using a phantom filled with tissue-equivalent fluid (density $=1.07$ g/cm^3) with the front window of the phantom 125 cm from the target. Using a 0.1 cc tissue-equivalent ionization chamber, we measured the depth for one-half maximum dose to be 10.2 cm corrected to unit density. A second measurement of kerma rate and depth for one-half maximum dose was made with a 6.0 cm polyethylene filter (density $=0.92$ g/cm^3) between the target and the collimator. With the addition of the polyethylene, the kerma rate was reduced to 0.21 rad/minute/microampere of beam current. The depth for one-half maximum dose was increased to 11.9 cm corrected to unit density. This depth dose compares favourably with a similar field size for cobalt-60 γ radiation at 80 cm SSD.

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*Work supported by N.I.H. contract 1 PO1 CA17419–01.

†Masonite Corporation.

Correspondence

(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

A COMPARATIVE STUDY OF SPECIAL PETROUS VIEWS AND TOMOGRAPHY IN THE DIAGNOSIS OF ACOUSTIC NEUROMAS

I would like to make two points of criticism regarding the conclusions reached by Dr. Osborn in his recent paper.

Firstly, radiation exposure to the eye cannot be advanced as a reason for not using tomographic methods for the investigation of acoustic neuromas. Since the publication by Chin *et al.* (1970), quoted in the paper, all tomographic studies of the petrous bone in the X-ray Department at the Royal National Throat, Nose & Ear Hospital have been performed in the postero-anterior position of the skull. This reduces the dosage received by the anterior cornea to less than 20 millirads per four exposures, using hypocycloidal tomography or zonography. These results are derived from our most recent monitoring. To put these figures in perspective, by the same method of dosage measurements (Lithium Fluoride sensors), a single Towne's projection taken on a standard skull table (2 mms. Al tube filtration) recorded a dose of 840 millirads to the cornea. The conclusion is that it is not tomography that produces unacceptable lens and cornea radiation exposure, but rather the use of antero-posterior radiographic positioning of the skull.

The second point concerns the question of false positives on I.A.M. studies. In our experience the commonest problem in this respect is the presence of large air cells in the petrous tip which may cause misleading appearances, particularly on plain X-ray and on zonography, and may be difficult to distinguish from erosive changes. Usually the problem can only be resolved by using thin section tomography—preferably hypocycloidal tomography in two planes. Lateral studies are particularly important in this situation and are often the most informative.

Our routine at the Royal National Throat, Nose & Ear Hospital in the investigation of patients referred with suspected I.A.M. abnormalities, is to use postero-anterior zonography as a screening procedure. These zonograms produce what is in effect a superior version of the per orbital projection (Lloyd and Wylie, 1971). If the zonograms are negative no further views are taken, but if there is any suspected abnormality then full hypocycloidal studies are made. These include P.A. and lateral tomograms and in addition axial zonograms of the petrous bones, which may be especially helpful in demonstrating erosions of the posterior lip of the porus acousticus. This system has proved an acceptable compromise in a department which undertakes over 700 I.A.M. examinations annually.

Yours, etc.,
G. A. S. LLOYD.

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THE EDITOR—SIR,

RADIATION DOSE MEASUREMENTS TO THE EYES DURING CEREBRAL ANGIOGRAPHY

British Journal of Radiology, *49*, 570–571

I am sorry to say that the mA values in our exposure table, where they relate to magnification angiography, have been given as double the true values; they should therefore read 50 rather than 100 and 62 rather than 125. This correction makes no difference to the radiation figures, but is necessary so that other workers are not persuaded that we have some new, super X-ray tube.

Yours, etc.,
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THE EDITOR—SIR,

THE COMPLICATION OF MYELOGRAPHY

We wish to draw attention to our experience concerning paraplegia following myelography in syphilitic patients. The patients were men of 43 and 52 years who had myelograms performed for backache; in each case Myodil was used. Both patients complained of severe pain in the back and legs immediately after the injection of the Myodil; this was followed by a stage of shock and both became completely paraplegic within two hours after examination. A full investigation was then carried out, but the only abnormal findings were V.D.R.L., T.P.H.A., and F.T.A. tests positive, and both patients were known syphilitics.

We therefore wonder whether syphilis was a predisposing factor to the adverse reactions and whether myelography is contraindicated in syphilitic patients.

Yours, etc.,
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THE EDITOR—SIR,

FETAL CERVICAL HYPEREXTENSION IN BREECH PRESENTATION

I read with considerable interest the article by Dr. J. G. B. Russell and Dr. Margaret R. C. Aird in the British Journal of Radiology of July 1976 on the above subject. It has been my experience over several years that hyperextension of the cervical spine of the fetus in the antenatal radiograph is sometimes associated with the presence of the umbilical cord being wound round the fetal neck and it may well be a cause of fetal distress during labour. A follow-up of these cases proved that in the majority, this was the correct assumption and I found it important to point out to my obstetrical colleagues the possibility of such a situation arising. Obviously, it is more easily seen in the breech presentation where one gets a "star-gazing" fetus, but it can also be sometimes suggested where the head is presenting by a brow presentation.

Yours, etc.,
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1976, *British Journal of Radiology*, *49*, 976

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

Computing Aids to Radiotherapy

A meeting organized by The British Institute of Radiology to be held on November 18, 1976 at the Institute House.

Further information from the General Secretary, The British Institute of Radiology.

A Radiobiology Work-in-Progress Meeting

To be held in the Institute House on Friday, November 19, 1976. Information from the General Secretary, The British Institute of Radiology.

Whole Body Counting and Scanning

A meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held November 24, 1976 at the Institute House. Further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Proliferation Kinetics

An all-day meeting organized by the Radiobiology Committee of The British Institute of Radiology, to be held on December 4, 1976. Further information from the General Secretary, The British Institute of Radiology.

British Medical Ultrasonics Group

The Annual Meeting of the British Medical Ultrasonics Group will be held at the University of Dundee on December 20–21, 1976.

Papers will be presented on all aspects of diagnostic ultrasound and there will be an associated commercial exhibition.

Further details and registration from: The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Effects of High LET Radiations

A radiobiology meeting to be held on January 21, 1977 at the Institute House, 32 Welbeck Street, London W1M 7PG. Further information from the General Secretary.

Radiology in the European Economic Community

A joint meeting organized by the Royal Society of Medicine (Section of Radiology) and the Royal College of Radiologists, to be held at the Royal Society of Medicine, London W1, on January 21, 1977. Details from the Royal College of Radiologists, 28 Portland Place, London W1.

Radioisotope Investigations of Diseases Involving the Endocrine Organs

An all-day meeting held jointly with the Endocrinology Society and organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on February 16, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Unorthodox Approaches to Fractionation

A meeting held jointly with the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology) on February 18, 1977. Information from the General Secretary, The British Institute of Radiology.

The British Institute of Radiology Annual Congress and Scientific Exhibition

To be held on April 14–15, 1977 at the R.I.B.A., London W1. Papers presented will include the "Silvanus Thompson Memorial Lecture" by Mr. G. N. Hounsfield, C.B.E., of EMI Central Research Laboratories.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiation Protection: An Example of Action Against Modern Hazards

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

The Mackenzie Davidson Memorial Lecture

To be given by Dr. David Ingvar, University of Lund on May 19, 1977.

New Horizons in Intensifying Screen Technology

An all-day meeting organized by the Industry Committee of The British Institute of Radiology on May 20, 1977 at the Middlesex Hospital Medical School, London W1. Registration details and information from the General Secretary, The British Institute of Radiology.

Use of Krypton Generators

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Middlesex Hospital Medical School, London, W1 on June 15, 1977. Registration and details from the General Secretary.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colegio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

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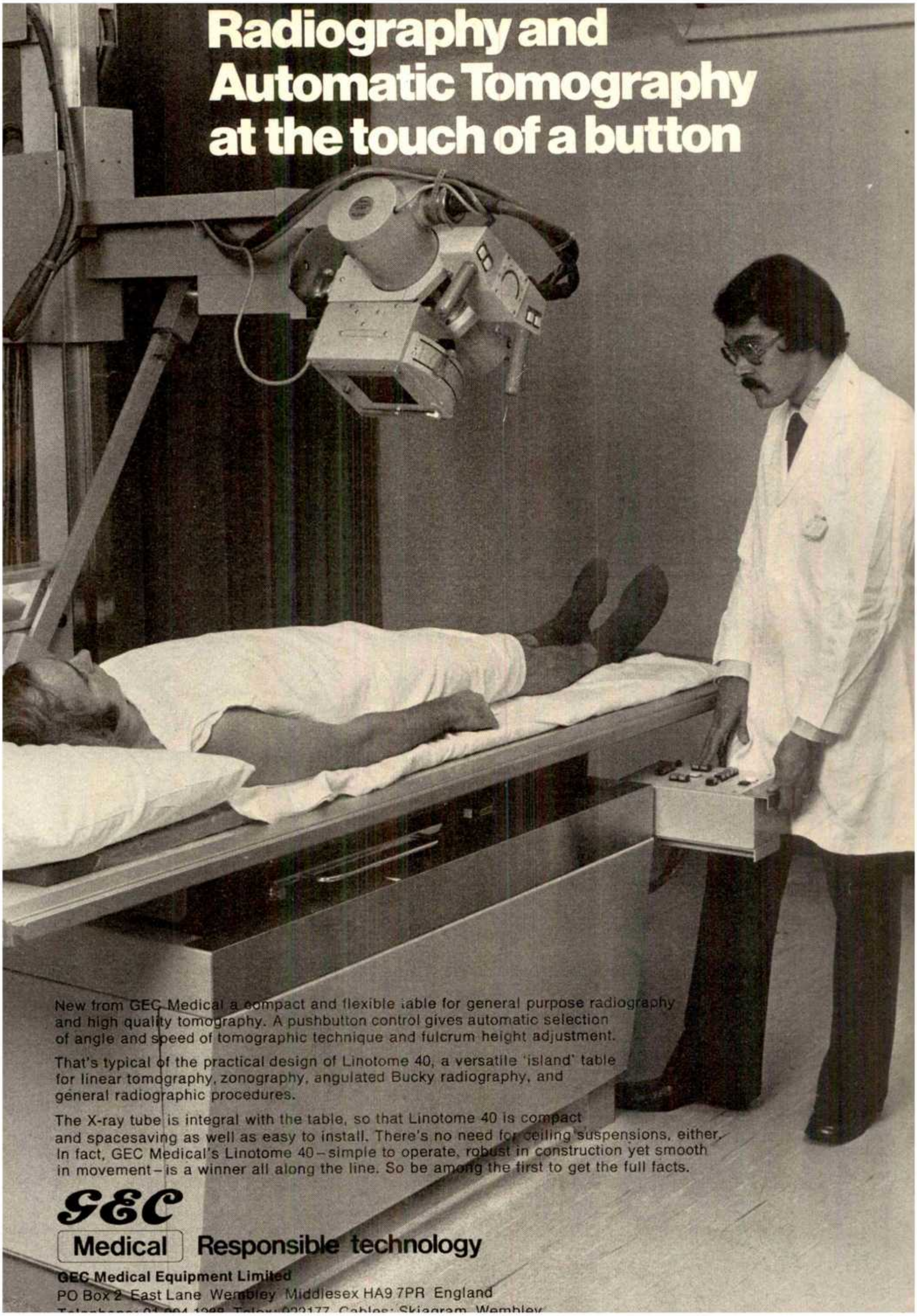

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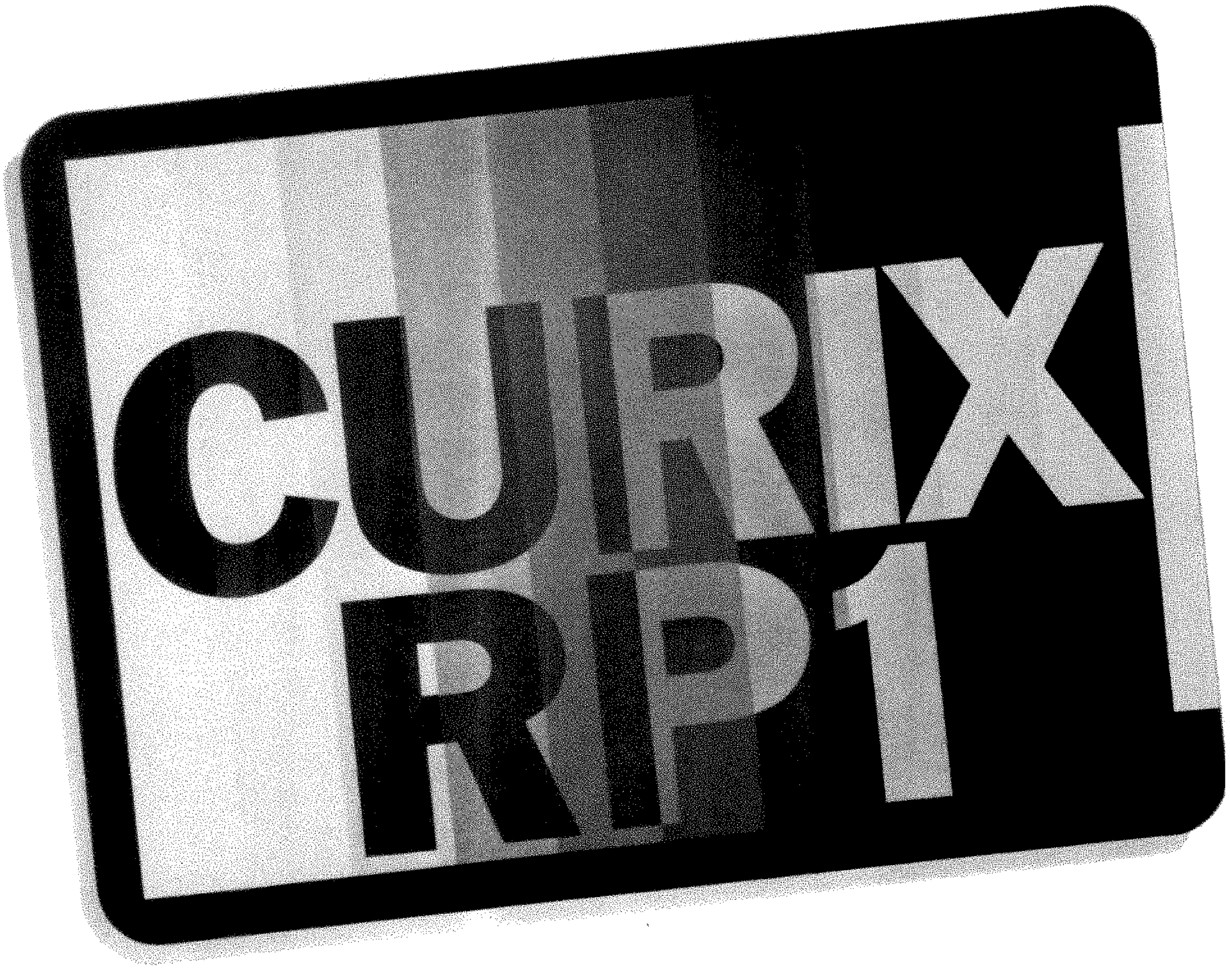

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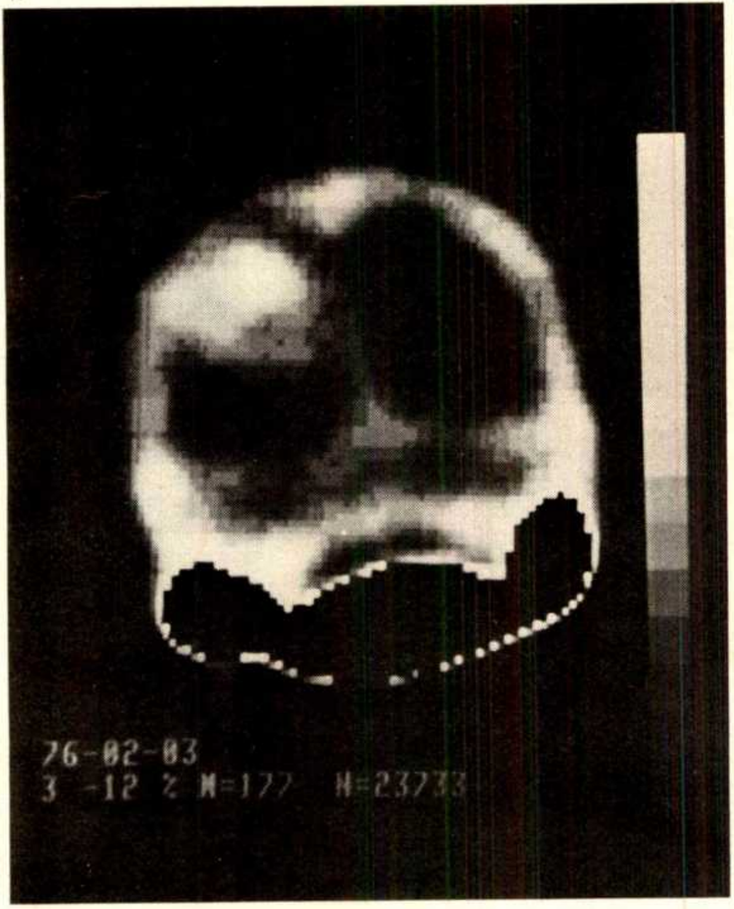

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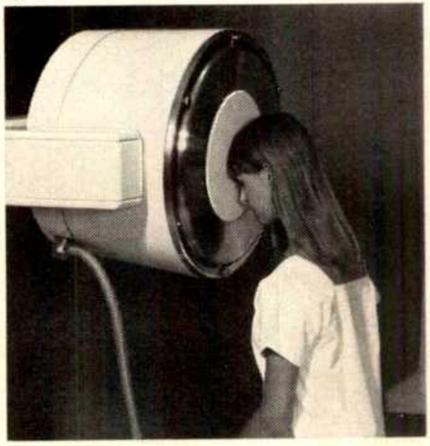

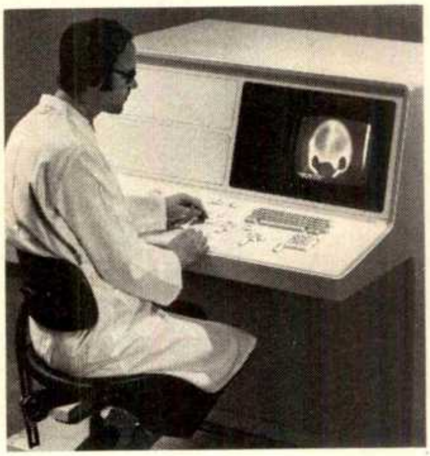

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2. Position for brain examination.
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Though varying greatly in size, neonates and adolescents both belong to the domain of the paediatric radiologist, thus special requirements are imposed on the radiological equipment used.
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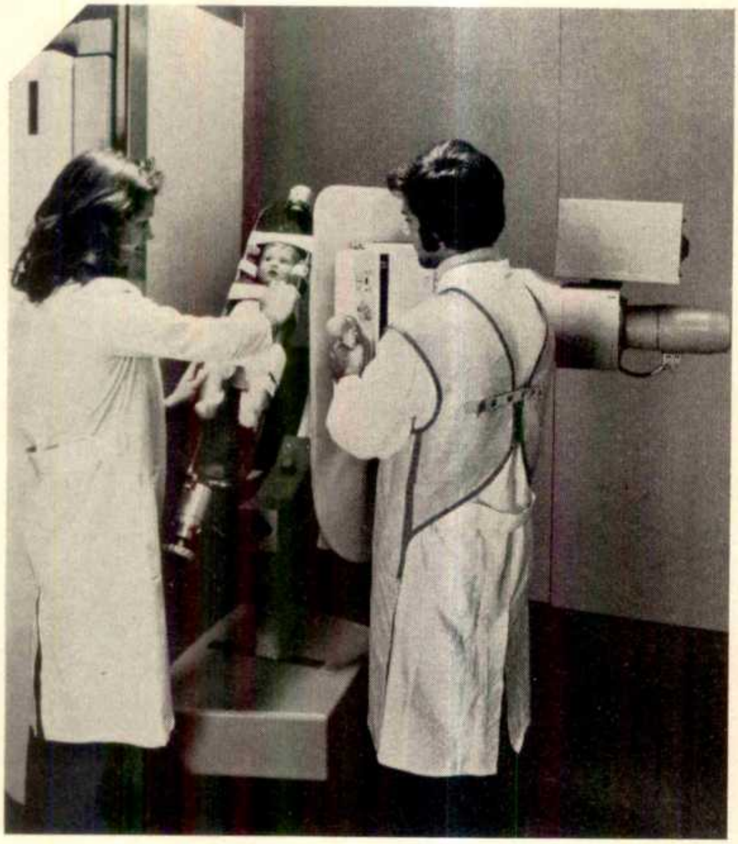

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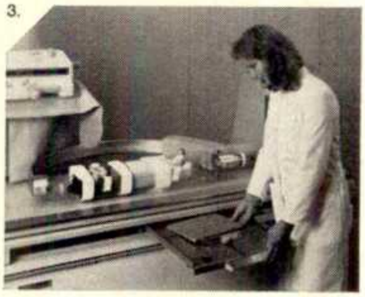

1. The change-over from examinations in adults to children is quite literally a matter of seconds. The paediatric supports are quickly installed and removed; parking when not in use is easy and convenient.
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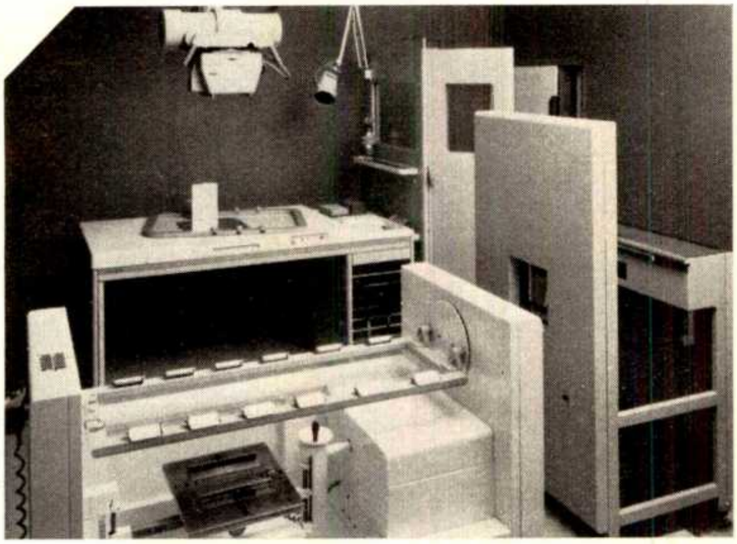

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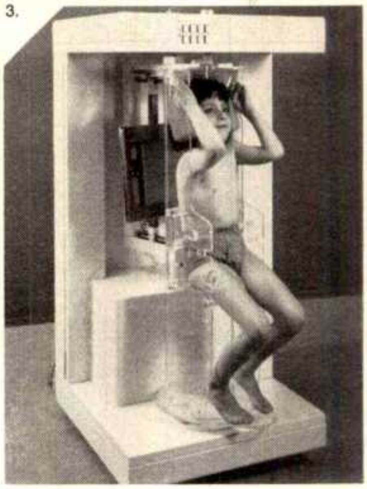

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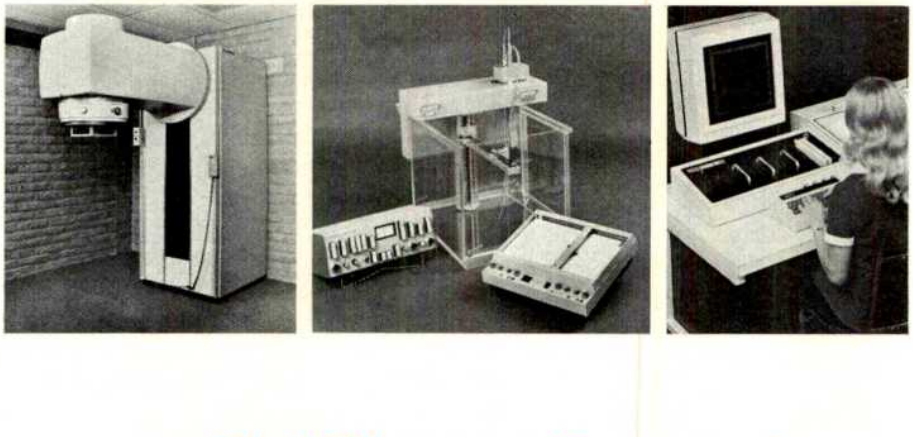

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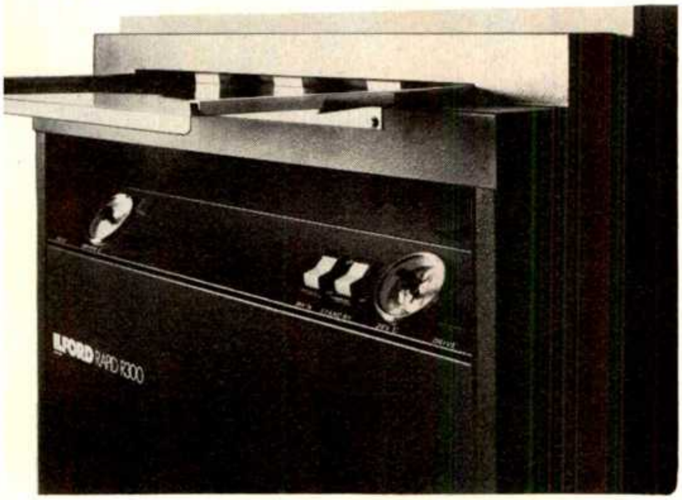

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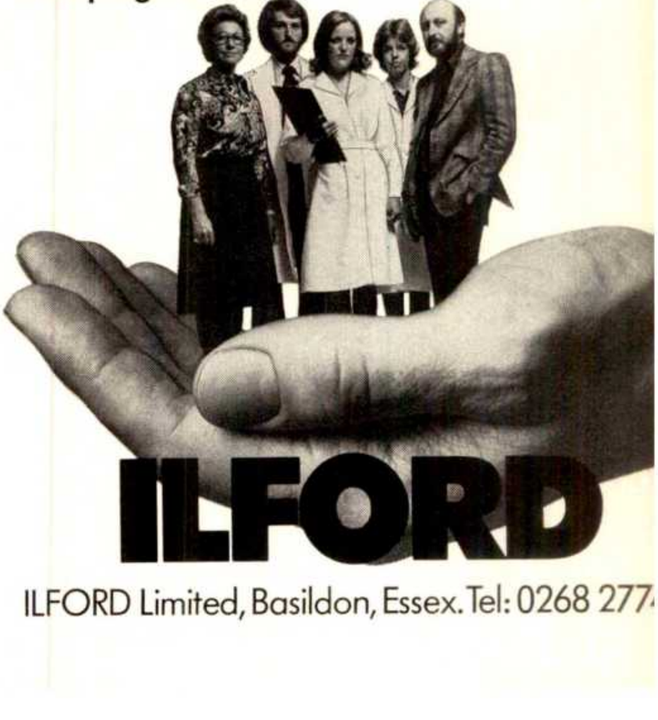

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The Philips Integrated Therapy Programme ensures increased efficiency in the modern radiotherapy department by having a common design philosophy, similarity of operational procedures and simplified service.

The programme embodies maximum reliability and patient safety. It incorporates a long-term plan providing the clinic and hospital with the essential equipment for today and the future.

The new Philips 5MV linear accelerator is the latest introduction to the Programme.

A machine that has been specifically designed for the radiotherapy department needing a unit for X-ray treatments when electron therapy is not required.

Fulfilling an important role.

For the smaller clinic, the SL.75/5 offers all the sophistication of the higher energy linear accelerators in the same series, but it has also been carefully designed to match other units in the 4–6MV range.

For departments where the higher energy machines are already in operation, the common design philosophy of the 5MV enables it to be readily integrated into the department.

All this makes the 5MV ideal as a primary treatment unit or a secondary unit for the larger overworked clinic.

This is what you can expect in performance.

The SL.75/5 will handle 60 patients a day.

The X-ray energy can be set in the 4–6MV range and is monitored and controlled by the same system that is used in the other Philips linear accelerators and so ensures accurate energy stability.

Dose rates at 350 rads per minute at one metre can be achieved at 5MV. (Equivalent to 550 rads per minute at 80cm.)

The maximum field size is 40x40cm at one metre F.S.D.

A 420° gantry rotation has been included to ensure rapid setting up of patient treatments.

All movements are motorised with variable speed control and have simultaneous movement capabilities.

There is also a choice of treatment tables. Either a high lift ram type or an above floor version. (A combination of table side supports and centre spine construction allows beam access from any angle.)

Safety as always.

A major aspect of the SL.75/5 design concerned safety.

The dual channel dosimetry system is backed by a timer. Select and confirm routines ensure maximum patient safety and reduce operational errors. And if required, a verification system can also be added.

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Dose and time LED displays are automatically maintained in the event of an electrical supply failure.

Find out more about the 5MV and the entire Philips Integrated Therapy Programme.

Here we have made a brief mention of just a few aspects that make the SL.75/5 an important addition to the Philips Integrated Therapy Programme.

The entire Programme includes cobalt units, localiser/simulator, a treatment planning system and ortho-voltage therapy units.

Philips are constantly developing new equipment for the highly specialised radiotherapy field.

If you would like to know more about the Philips Integrated Therapy Programme,
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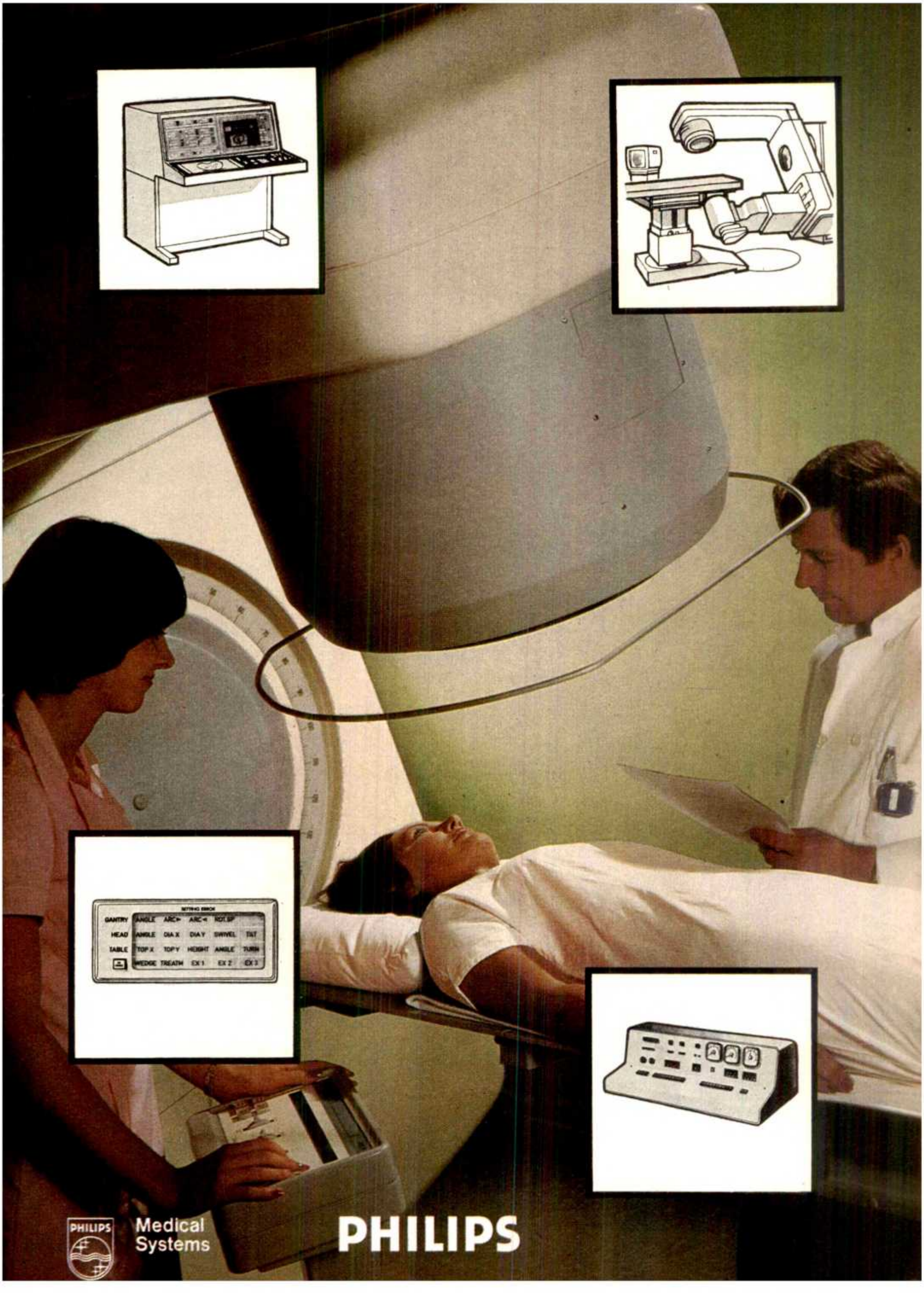
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angio U.P.I.

U–arm
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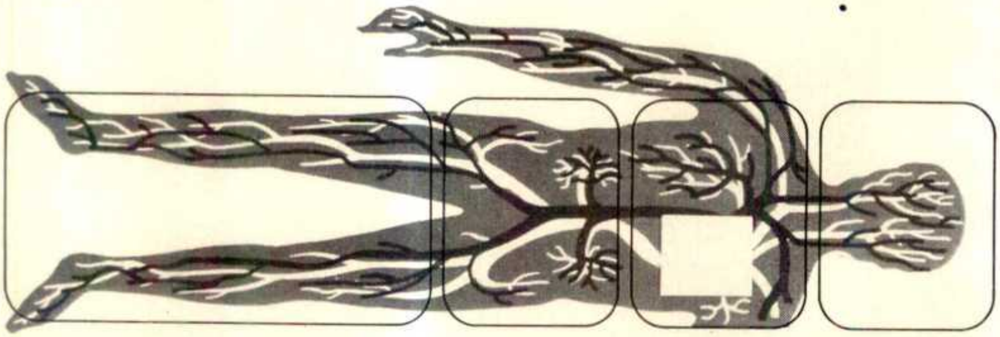
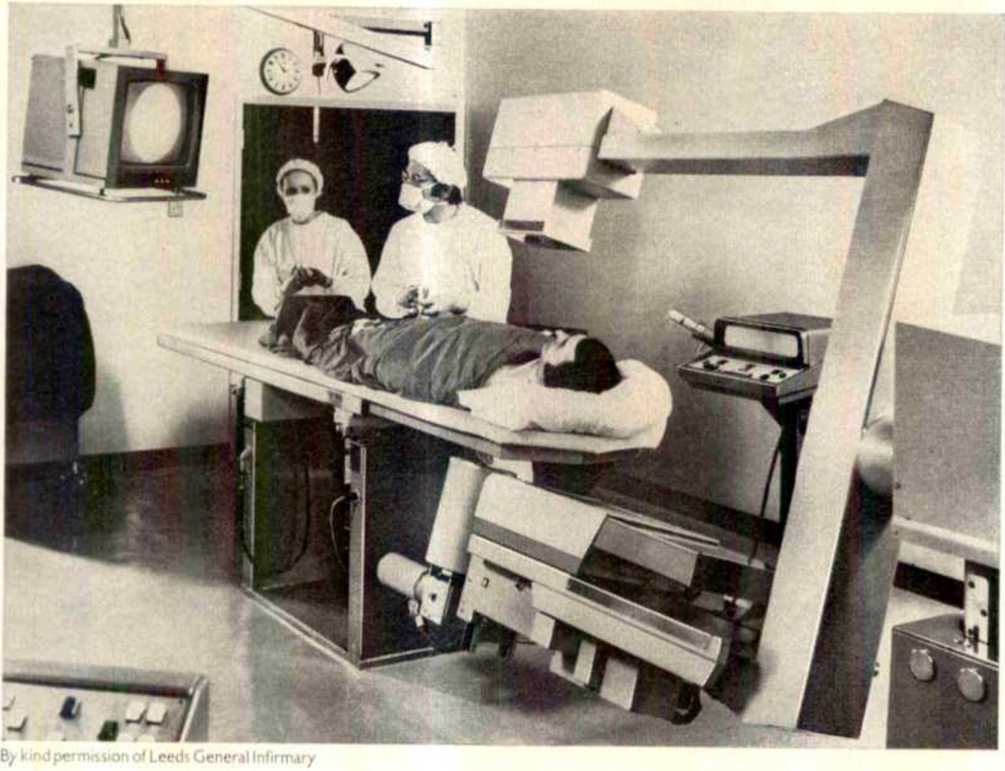
Image intensifier

A unique system for general angiographic examinations





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The Angio U.P.I. is the first angiographic apparatus to offer all these features:

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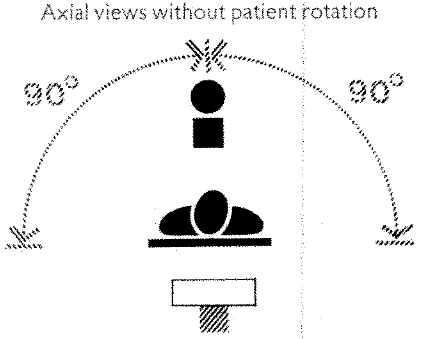

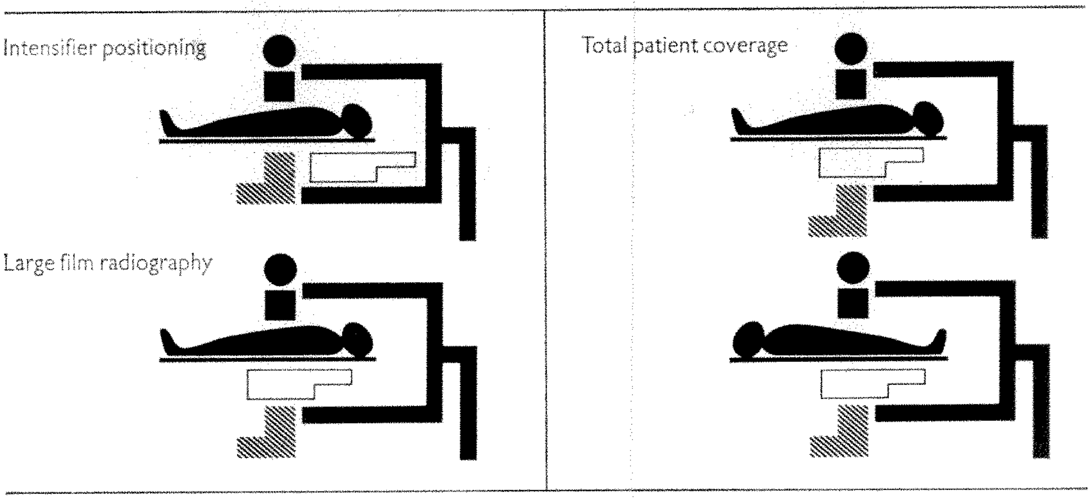

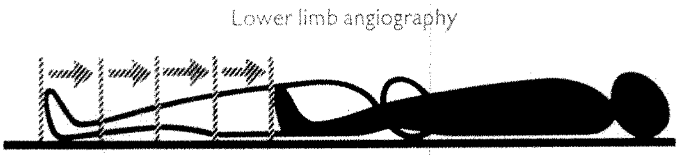

Further details on the Angio U.P.I. system are available from
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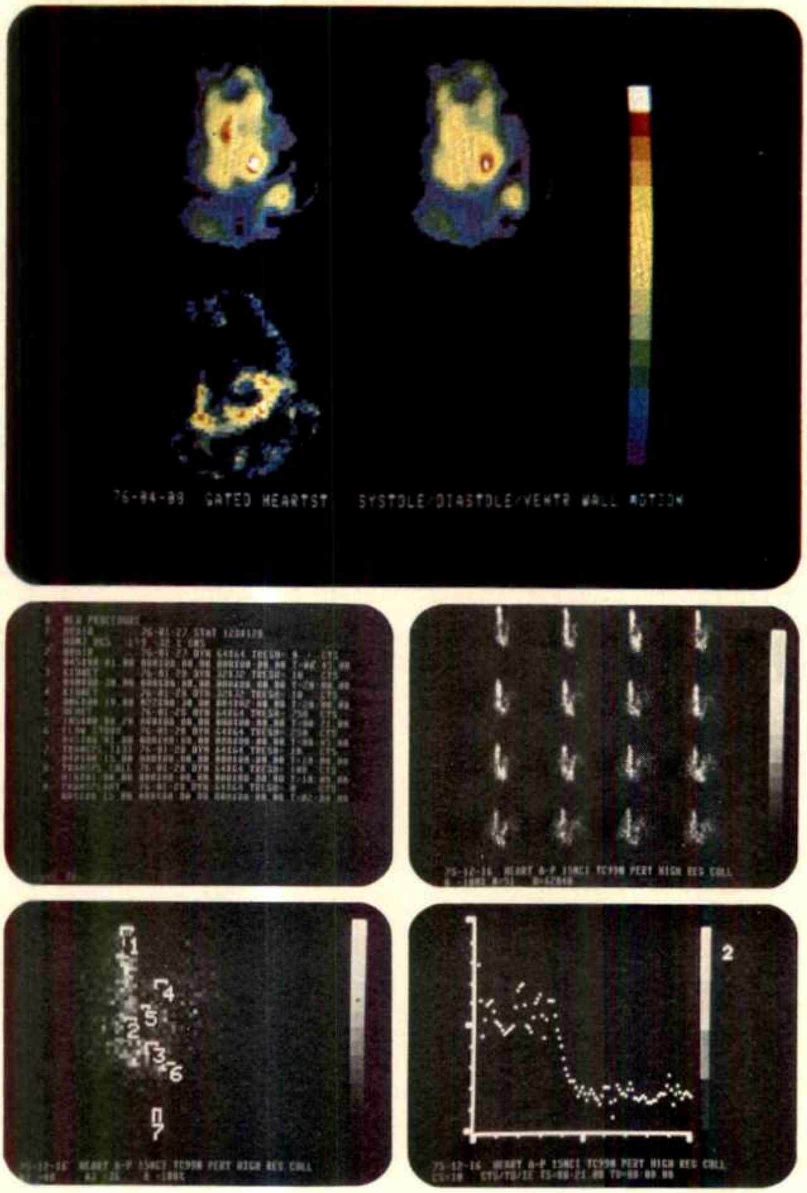
Indepth
evidence



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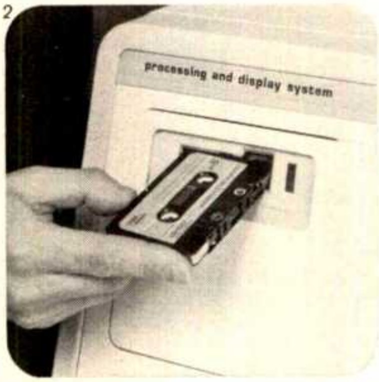
Modern radio-isotope techniques enable non-invasive vizualisation of ischemic areas of the heart . . . and processing the mass of data obtained is a task for a Philips Processing and Display System. In the colour video display, the two upper images show the heart in systole and diastole, acquired under ECG gating, while the third image, corresponding with the motion of the ventricular wall, is generated by a special program. If desired the user can also compose special programs – by simply linking existing sub-routines – and call them at any time by pressing the relevant program number.
Replay of the total study with 16 images at a time enable the optimal replay mode to be selected. Replay can be interrupted for the selection of regions of interest from which the computer calculates the time/activity graphs corresponding with the organ function.

This indepth evidence admirably illustrates the effectiveness of the Philips Processing and Display System in providing rapid quantitative and qualitative diagnostic information obtained during dynamic investigation in nuclear medicine.

The system employs a Philips mini-computer with a 32k 16-bit memory which, together with disc-operated software programs, provides considerable processing speed and flexibility. Furthermore, it has been designed specifically for use by medical personnel and program execution requires no specialized knowledge of data processing techniques.

1

2



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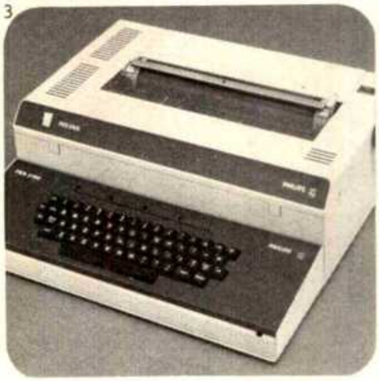

1 **Direct access** to disc-stored programs covering a complete range of routine examinations is by means of ergonomically grouped key arrangements; the results being immediately displayed on the 30 cm black- and- white video monitor. The system can be extended with a colour monitor. Frequently used procedures can be combined to form new programs. In cases where a single key offers the choice of more than one routine, the program assumes a 'question-answer' mode enabling the operator to make a suitable choice. Incorrect operation is not possible. If a non-acceptable procedure is inadvertantly selected, the keyboard is immediately blocked and an 'error' condition displayed on the monitor.
2 **Software programs,** including standard as well as improved routines, are introduced via the system's built-in compact-cassette recorder. This facility also enables results to be recorded for eventual image playback and appraisal.
3 **FORTRAN IV option.** The capability of Philips Processing and Display System can also be extended to solve special problems. In such cases data can be pre-processed in the convenient PDS way and further analysis carried out using the FORTRAN IV option. Programs can be written in FORTRAN language by the user and results monitored on the PDS display or printed-out on the same terminal that is used to enter or retrieve the FORTRAN program.

Part of a complete program of nuclear medicine equipment and systems, and fully supported by an international service organisation, the Philips Processing and Display System represents the perfect integration of operational simplicity and efficiency with applicational flexibility and reliability.

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If you would like further evidence on Philips Processing and Display System, or on any other equipment in our nuclear medicine programme, complete this coupon and send to:
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AUSTRALIA

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ROYAL BRISBANE HOSPITAL
DEPARTMENT OF RADIOLOGY

DEPUTY DIRECTORS (3 positions)

Applications are called for the positions of Deputy Directors of Radiology (3 positions) in the Department of Radiology at the Royal Brisbane Hospital. The appointees will work under the general direction of the Director of Radiological Services to the Royal Brisbane Hospitals Group. The Royal Brisbane Hospitals Group consists of the Royal Brisbane, Royal Children's and Royal Women's Hospitals. The appointees will have close association with the Radiologists at the Royal Children's Hospital, each of the three positions will have special responsibilities. It is envisaged that the special responsibilities will be–

1. Neuro-radiological Services
2. Special Procedures
3. General radiological services Casualty radiological services and Obstetrical radiological services.

Applicants should state their special interest or preference for any of the three positions.

The Royal Brisbane Hospital has some 1,100 beds and the Department of Radiology performs some 130,000 procedures per year. The equipment in the Radiological Department is at present being up dated and the department itself is being extensively enlarged by an extension to the new department in an adjoining new block.

In the General Department all types of radiological procedures are carried out and it is contemplated that ultrasound and body scanning will be added as soon as these procedures become an established reality.

The Neuro-radiological Department is situated within the Department of Neurology and Neurosurgery and is equipped with a Mimer III Neuro-radiological Unit and an E.M.I. Head Scanner.

In the Department, as well as the Deputy Directors, there is an establishment of a Director, 8 Staff Radiologists and 11 Registrars in training. Close co-operation is expected between the department and the newly created Chair of Radiology within the University of Queensland.

The positions are permanent after a period of 12 months probation. Superannuation, 5 weeks annual leave, sick leave, conference leave and overseas study leave are provided.

Salary is $A.29,458 per annum.

Further information available from the Agent-General for Queensland, 329 The Strand, London WC2 0LZ to whom applications should be sent giving full details of qualifications, age and experience, together with names and addresses of three referees. Closing date 18 February 1977.

BIOLOGICAL PRODUCTS IN THE TREATMENT OF CANCER

An open symposium to be held by the International Association of Biological Standardization

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Topics

Principles governing the use of biological preparations in the treatment of cancer
Materials B.C.G., C. parvum, Interferon, etc.
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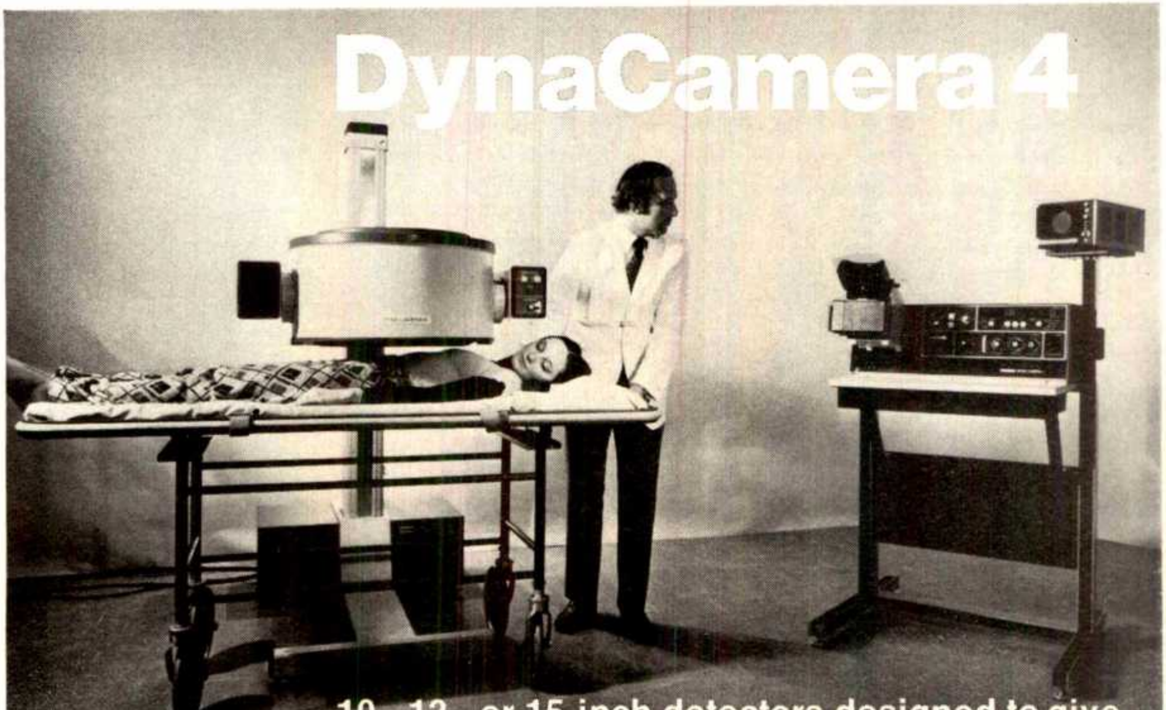
Quality control
Mode of action
Immunology
Pharmacology
Experimental oncology
Toxicology in animals
Clinical relevance of experimental data and design of trials
Clinical Studies

Further information and registration forms may be obtained from the Organizing Secretary, Dr. A. H. Griffith, The Wellcome Research Laboratories Langley Court, Beckenham, Kent.

Persons interested in presenting papers at this symposium are asked to submit the proposed title to the Organizing Secretary before December 31st, 1976.

Progress in Computerized Tomography

The Department of Diagnostic Roentgenology, Mayo Clinic, announces a 2½ day continuing education course entitled, "Progress In Computerized Tomography". The course will be held on May 25, 26, and 27, 1977, at the Mayo Clinic in Rochester, Minnesota. The program will emphasize computerized tomography of the body but will also include certain aspects of CT physics and economics and will include certain aspects of computerized tomography of the head and breast. The course is approved for AMA Category I credit on an hour for hour basis. Registration fee is $200. For further information contact Patrick F. Sheedy II, M.D., CT Course Director, or Robert R. Hattery, M.D., David H. Stephens, M.D., and O. Wayne Houser, M.D., Co-directors, Mayo Clinic, Mayo Foundation, Rochester, Minnesota 55901.



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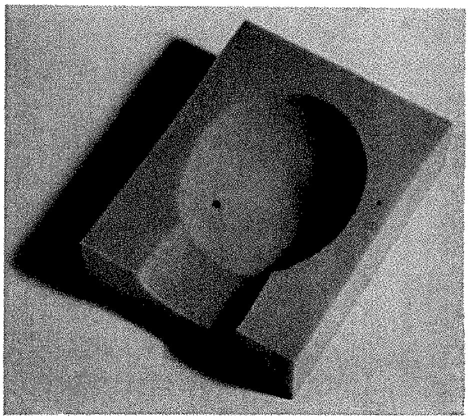

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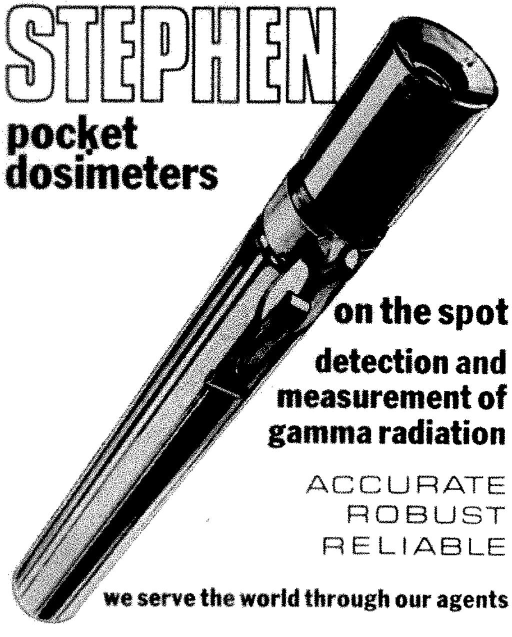

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Inquiries should be directed to:
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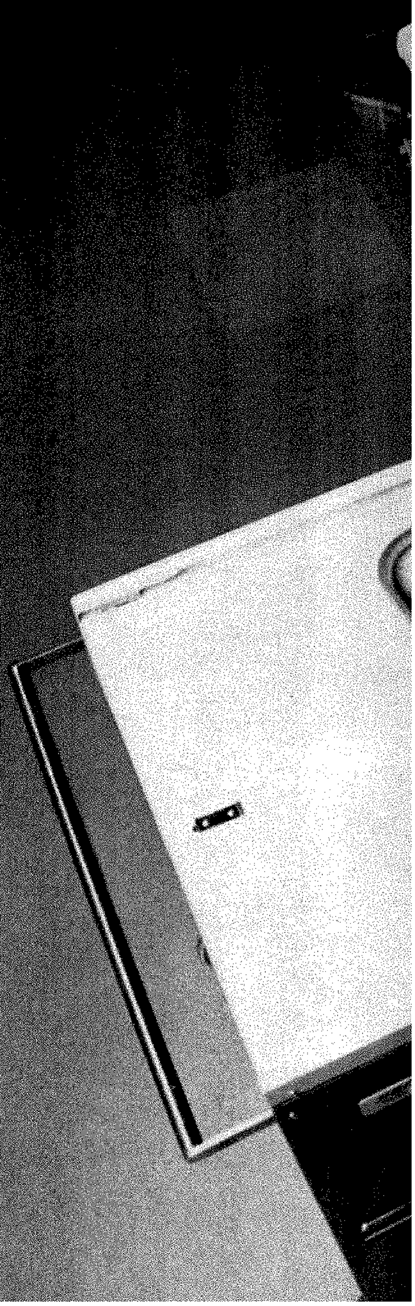

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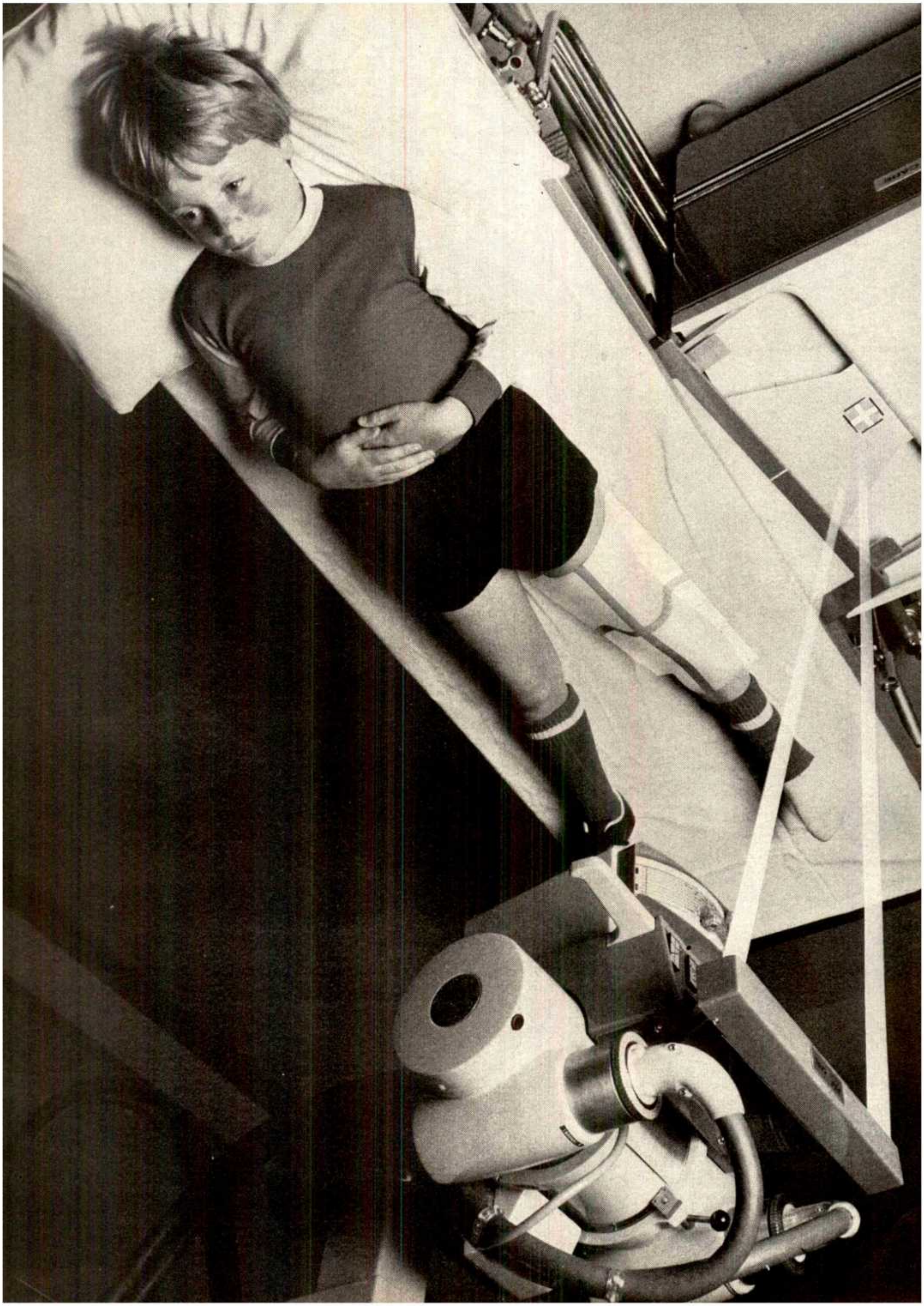

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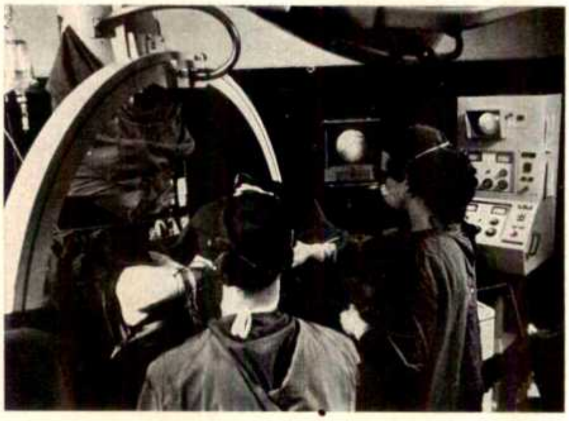

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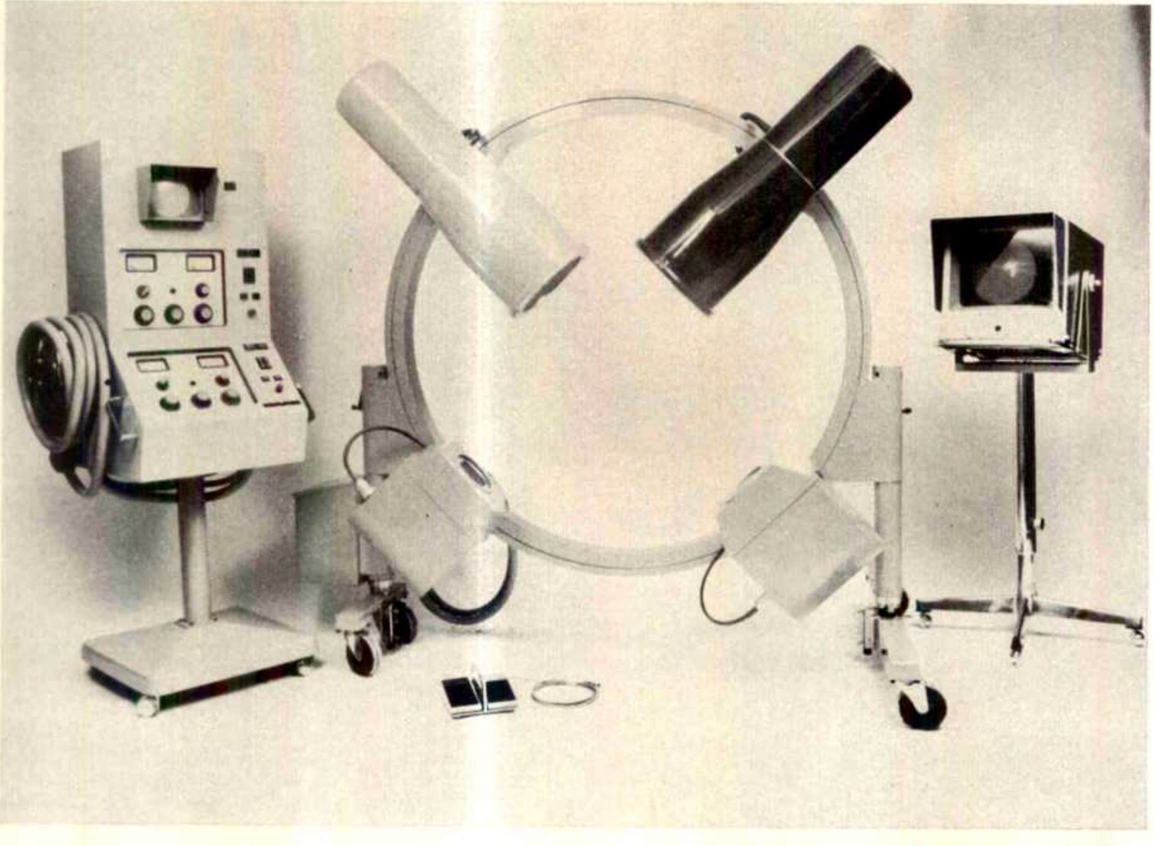

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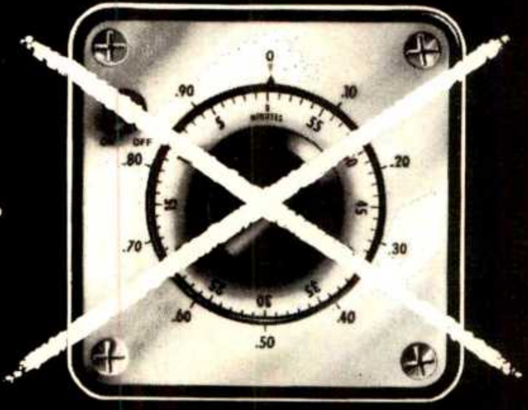

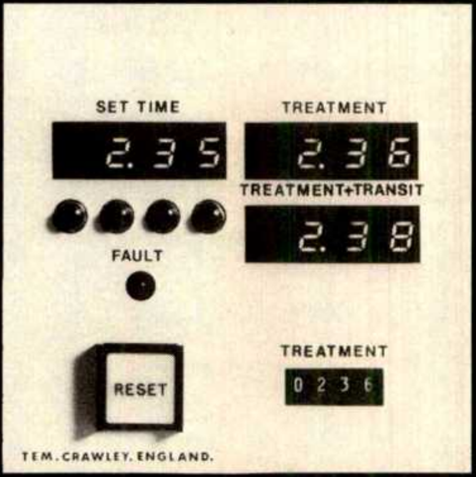

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A. Body Imaging – Clinical Comparison
1. The Head
2. The Chest
3. The Abdomen

B. Departmental Organization
1. Survey of Current Facilities
2. The Case for the Integrated Department
3. The Case for the Specialized Department

C. Education

This one-day meeting will be held in conjunction with the meeting of the Board of Trustees of the Society of Nuclear Medicine.

The program will be approved for credit toward the AMA Physicians' Recognition Award under Continuing Medical Education Category 1 through the Society of Nuclear Medicine.

For further information, please contact:

Edward V. Staab, M.D., Department of Radiology, Division of Imaging, North Carolina Memorial Hospital, Chapel Hill, North Carolina 27514.

The British Journal of Radiology
REVIEW ARTICLES

The Possibility of Hazard in Medical and Industrial Applications of Ultrasound, by C. R. Hill	50p
An Evaluation of Conventional Radiography in Acquired Heart Disease, by R. G. Grainger	50p
The Plain Chest Radiograph in Congenital Heart Disease, by K. Jefferson	70p
The Kinetics of Tumour Cell Proliferation and Radiotherapy, by M. Tubiana	75p
Radiation Therapy in Diseases of Larynx, by R. Morrison	75p
The Radiological Diagnosis of Adrenal Tumours, by D. Sutton (April 1975)	75p
Bone Scanning, by M. V. Merrick (May 1975)	75p
Tumour Imaging Radiopharmaceuticals, by A. H. F. Paterson and V. R. McCready (July 1975)	50p
Pharmaco-radiology in Barium Examinations with Special Reference to Glucagon, by L. Kreel (September 1975)	60p
The potential of californium-252 in radiotherapy, by E. J. Hall and H. Rossi (October 1975)	75p
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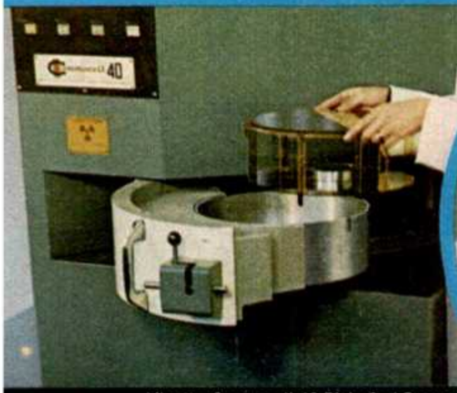

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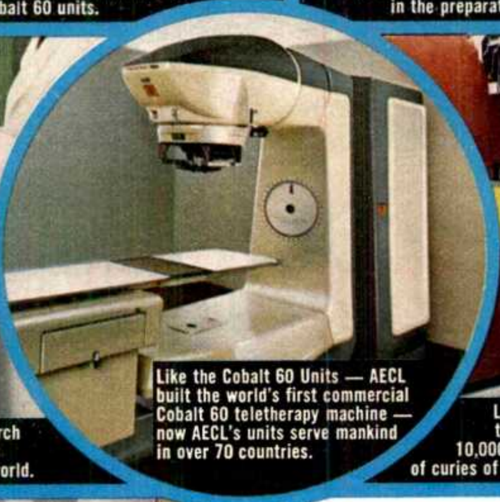

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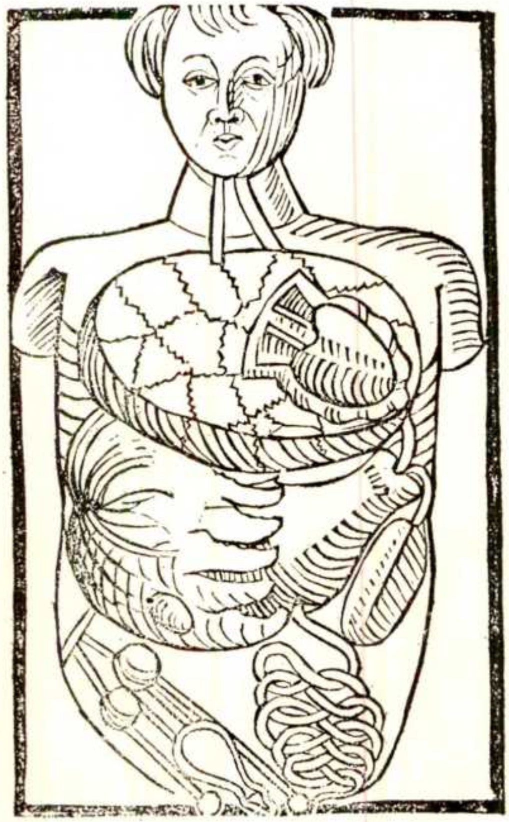

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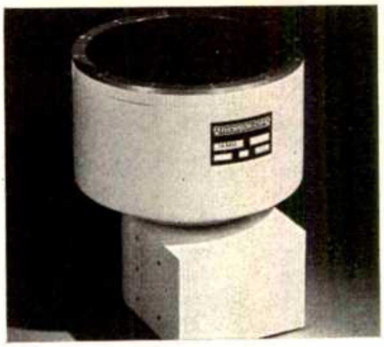

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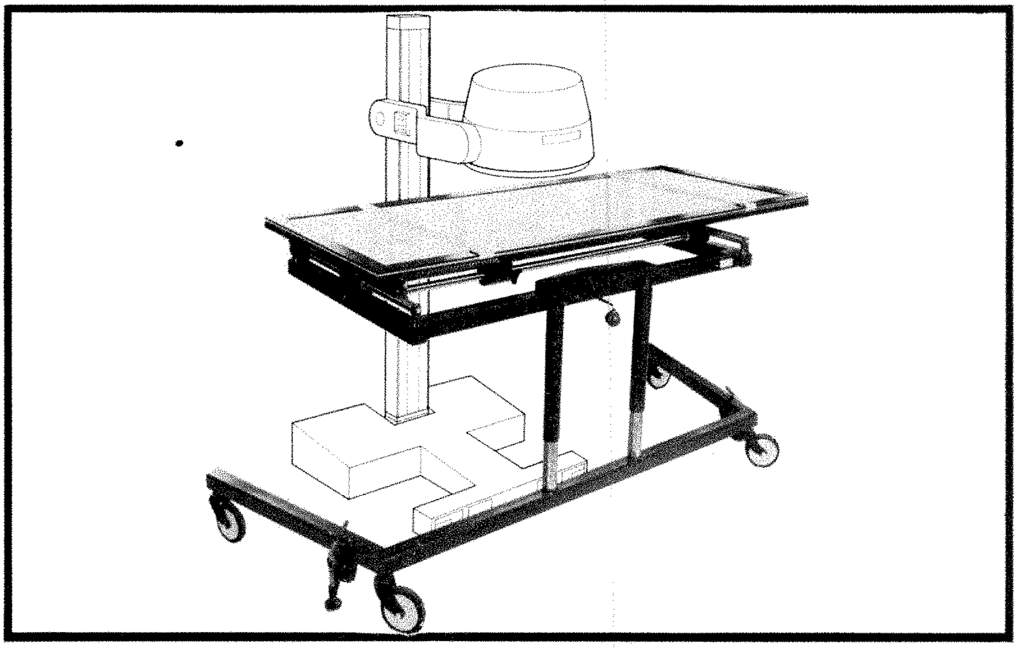

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British Journal of Radiology

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February issue Copy date Friday, 17 December

Issues after February will have a copy date of 1st of the preceding month instead of the 5th.

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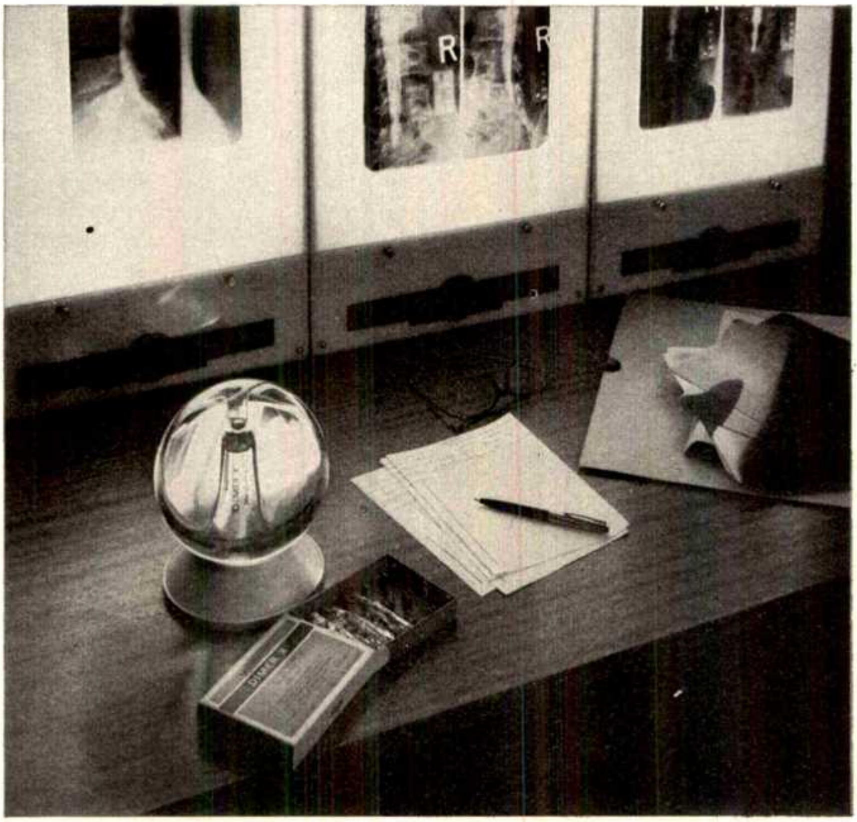

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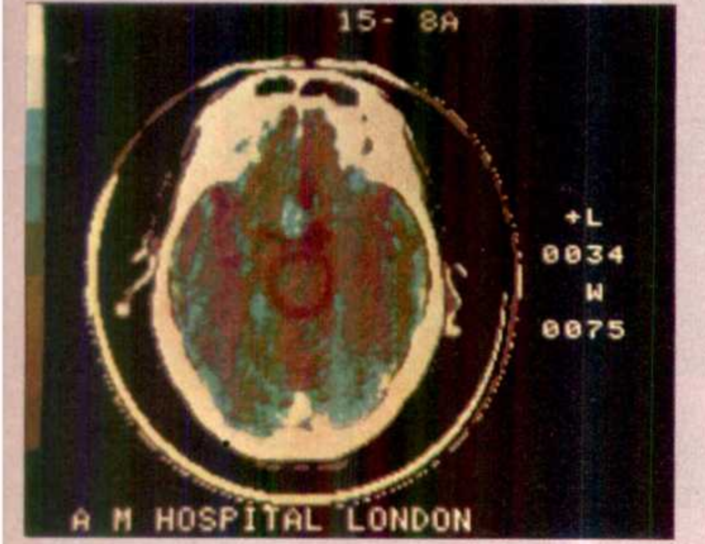

Patient Code 15, 8A.

Patient suffering from hypopituitrism. The EMI-scan shows a pituitary adenoma. The scan, taken after the injection of contrast, clearly shows the suprasellar extension into the chiasmatic cistern.

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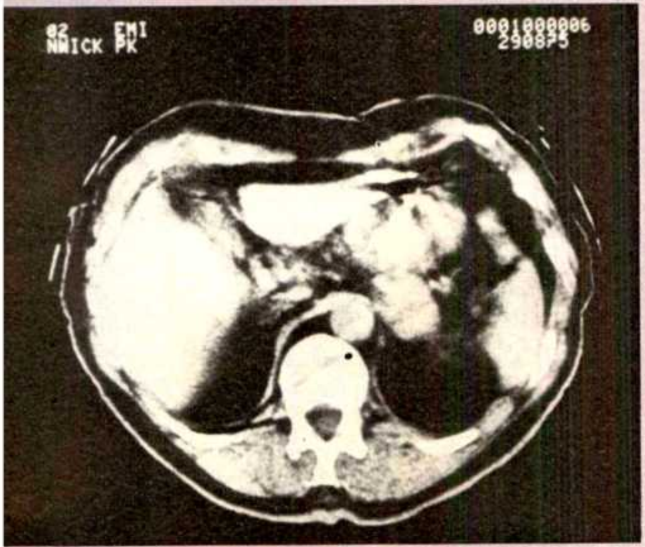
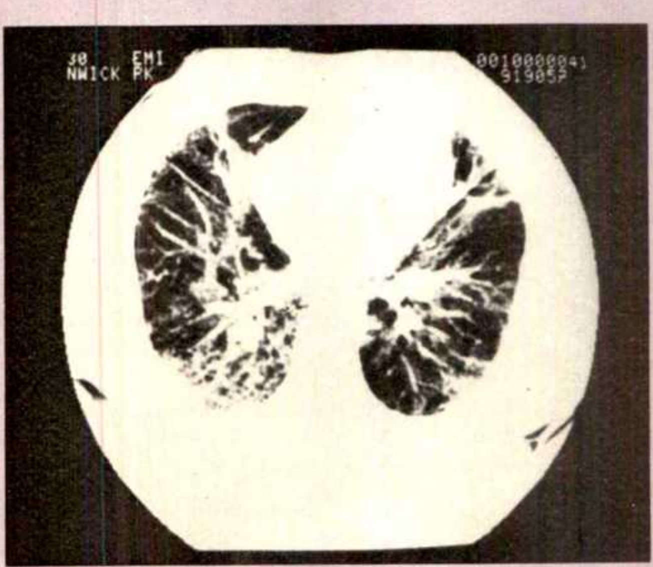
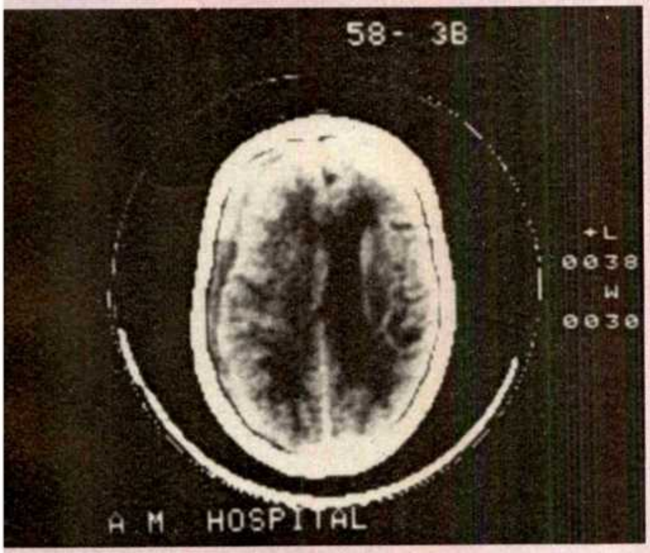


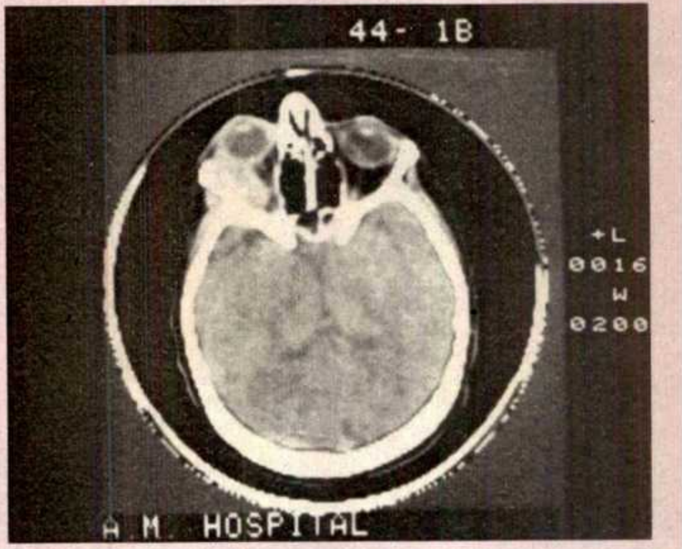
can 02.
can through 1st lumbar vertebra, demonstrates pancreatic yst.



Scan 30.
This scan clearly demonstrates interstitial fibrosis in the lungs. Due to the short scan time of the CT5005, the patient was able to suspend respiration for the duration of the scan, thus allowing the lung vessels to be clearly demonstrated without blurring.



atient Code 58, 3B.
9 year old female with a history of two falls in the month revious to admission. She was admitted in a confused and rowsy state. The EMI-scan clearly demonstrates a left ubdural haematoma.
Note: Scan taken in "high sensitivity" mode. Note the clear elineation between grey and white matter.



Patient Code 44, 1B.
Young male patient with a 12 month history of increasing proptosis and limitation of lateral occular movements. Lately he has suffered from conjunctival oedema. The EMI-scan demonstrates a mass in the lateral section of the left orbit, with early calcification visible within the mass. Note the detail visible in the orbital regions.

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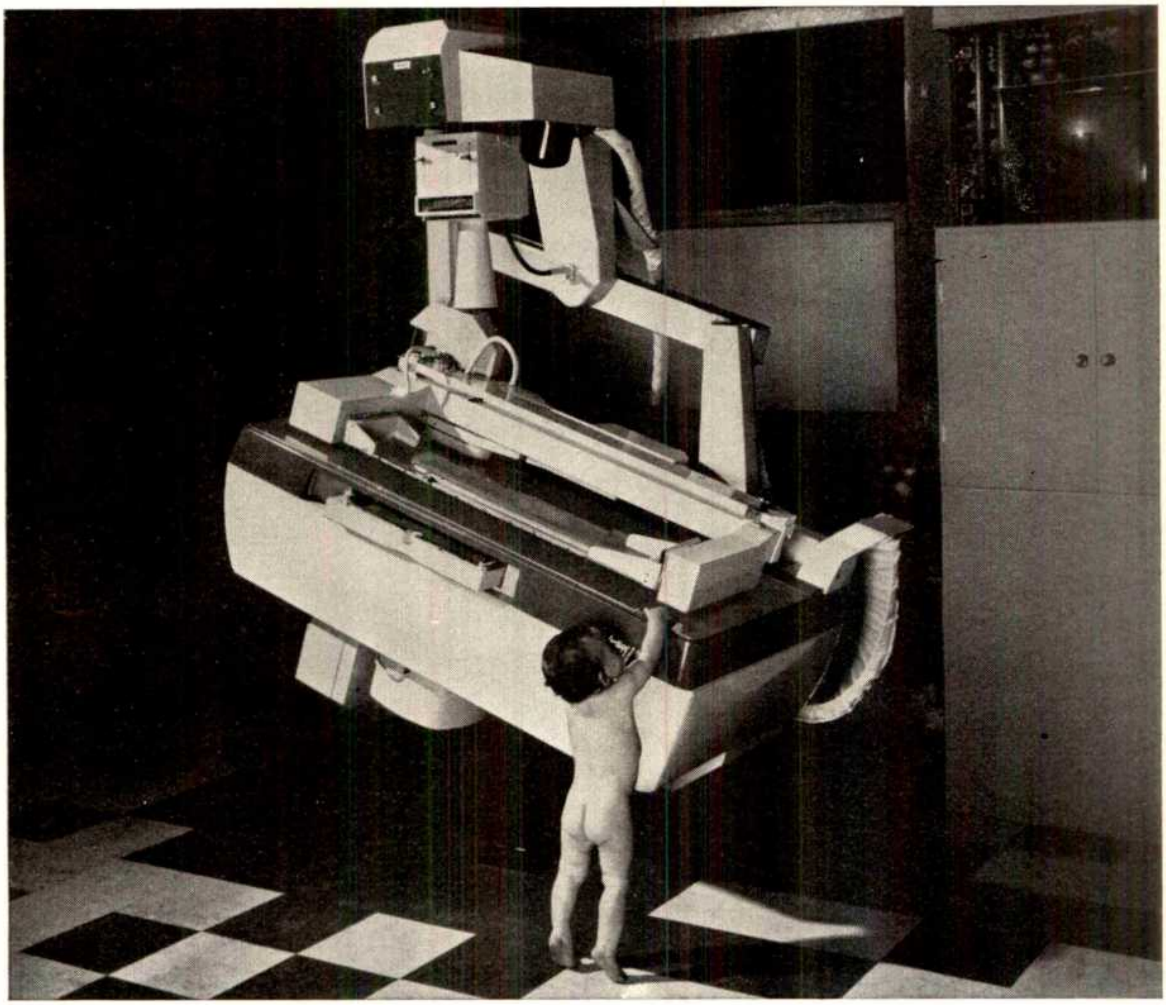

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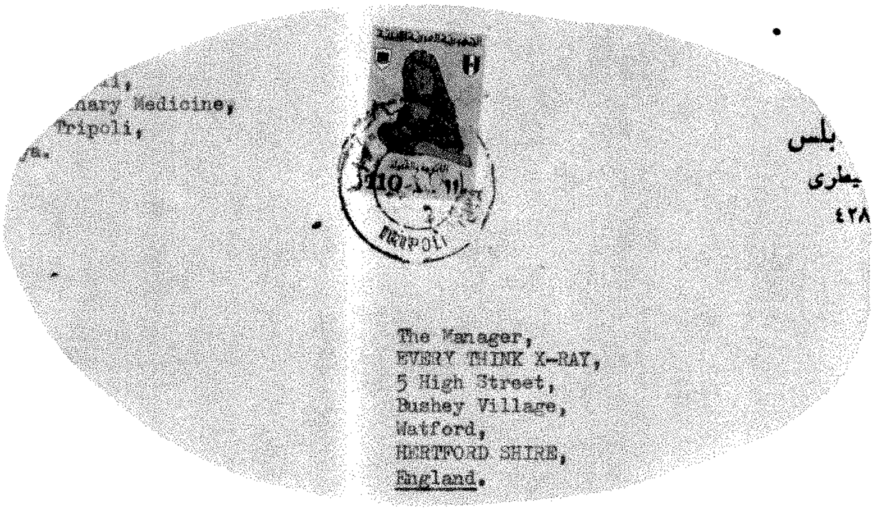

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The Pathogenesis of Reflux Nephropathy

By Professor C. J. Hodson, T. M. J. Maling, P. J. McManamon and M. G. Lewis

The association between vesico-ureteric reflux and renal damage has been recognized for some time, but it has usually been assumed that the damage is due to infection promoted by the reflux. However, observations by Rolleston and his colleagues in New Zealand have indicated a link between the severity of reflux and renal damage. Furthermore they have suggested that reflux penetrating into the renal substance is the factor most likely to explain the production of renal scarring.

These observations have been given a firm experimental basis by Professor Hodson and his associates. Their careful work on the growing pig has shown that the sites of intra-parenchymal or intra-renal reflux (I.R.R.) are the sites of subsequent and atrophy. I.R.R. only occurs above a critical pressure level; reflux at lower-pressures produces no evident damage. Infection aggravates scarring, but in the presence of I.R.R., scarring can occur with sterile urine.

The work set out in this monograph has wide practical implications, and is of interest to paediatricians, nephrologists, urologists, radiologists and others concerned in the management of patients with urinary tract infection.

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The British Journal of Radiology

Radiology now

Dynamic bladder studies

"Persisting stress incontinence following surgery: cystogram please" is a request to strike despair into many radiologists. What useful information is to be gleaned here from the micturition cysto-urethrogram (MCU)? Or from adult MCUs in general? How good are we at diagnosing bladder outflow obstruction by this examination, or explaining common presenting symptoms like frequency, urgency or incontinence?

Not very good, it must be said. It is instructive to inquire why this at times inconclusive, lumbering investigation in the adult turns so readily into a highly rewarding, delicate study in the child. The questions asked there are of course different. With the common presenting problem of childhood urinary infection we want to know about vesico-ureteric reflux, about major bladder disarrays like diverticula, and in boys about outflow obstruction. These are apt questions for the MCU, so they are answered. Bladder outflow obstruction in boys is usually sited in the urethra well below the bladder neck (*e.g.* urethral valve). Watching opaque medium passing briskly through a distensible tube of predictable calibre like the urethra is a good way of detecting obstruction along its length. Contrast this with the common questions we have to ask about adult MCUs: is bladder behaviour abnormal, or is there outflow obstruction at or just below the bladder neck? Is it likely that we could learn much about the action of a balloon or its neck by watching its contents pouring out?

Dissatisfaction of this sort has led to the development of functional studies alongside the MCU. Radiologists will not need persuading about the importance of understanding dynamic events in their work: in the heart and pulmonary circulation, for instance, the interpretation of chest films has clearly been advanced enormously by haemodynamic insights. For the bladder, some insights can be gained simply from the armchair. The significance of residual urine seen after voiding is an example. If there is outflow obstruction, the bladder will work harder, leading to hypertrophy of its muscular wall. For a time, it will be able to cope, expelling all the urine against considerably increased resistance. During this compensated phase of bladder outflow obstruction, voiding pressure will be abnormally high, but there is no residual urine. Thus the absence of this X-ray sign can never exclude even severe obstruction. Eventually the bladder fails, no longer able to empty all the urine. In this decompensated stage of outflow obstruction, residual urine is seen, and voiding pressure may no longer be so high.

In dynamic MCU work, bladder pressure and urine flow rate are recorded during bladder filling and voiding (Bates and Corney, 1971). A tiny per-urethral catheter measures total bladder pressure. This is made up of the intra-abdominal pressure and the activity of the bladder (detrusor) muscle. Because we want to study detrusor rather than abdominal muscle behaviour, the patient also needs a small rectal catheter in place for monitoring intra-abdominal pressure. Detrusor pressure is obtained by subtraction of the two. The several traces are best projected continuously alongside the fluoroscopic image during the MCU. The combined picture is recorded onto videotape, for later play-back and study of how the bladder looks and works (Whiteside, 1972; Turner-Warwick *et al.*, 1973).

A diagnosis like outflow obstruction can then be made with confidence on the classical functional criteria of raised proximal (detrusor) pressure and reduced (urine) flow rate. The synchronous MCU will show the level of obstruction. In general the MCU image is a vital comment on the dynamic data, and both are needed for complete diagnoses.

Some patients with bladder symptoms suffer from inappropriate detrusor contractions. Undetected on the MCU image, these are shown as abnormal detrusor pressure waves during bladder filling. They may be provoked by standing up and by coughing. This precise, testable notion of the "unstable

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bladder" (Bates, 1971) is an attractive advance on the older, vague idea of an irritable bladder syndrome. Finding patients with unstable bladders is a worthwhile exercise, if only to obviate pointless surgery. Thus the lady in the first line above, with troubles persisting after her operation, will probably need a combined pressure-flow MCU. We may find that she still has pure stress incontinence with an incompetent outflow tract on raising abdominal pressure. She could then benefit from further bladder neck surgery. But this is not so if she leaks urine because her coughing fires off an inappropriate detrusor contraction, *i.e.* if an unstable bladder is now the basis of her incontinence. In men, instability may complicate outflow obstruction. Relieving the obstruction (*e.g.* prostatic resection) usually cures the unstable bladder also, but if it does not the patient may still have complaints, perhaps put down to incomplete surgery.

The ability of the combined study to identify these problems and to direct patients toward proper management is a great boon. Surgeons are coming to recognize this, and radiologists are under pressure to provide more complex MCU facilities. With expertise the combined examination takes only a little longer than a standard MCU. The cost of additional equipment will vary very considerably, depending on what is already on the ground in any department.

It is easy to paint a beguiling picture here, and right to balance it with caution and common sense. Much more is needed for good work in this field than a little extra time and add-on equipment. For achieving any expertise and quality, devoted repetitive teamwork is required, involving the interested urologist and radiologist as well as nurses and technicians. Patients should properly be referred to this team for consultation. The radiologist who attempts to set up a urodynamic service in isolation will probably be used as a technician alone. Patients will be referred to him for "the test" rather than for an opinion, and little will be learnt. Such dispiriting settings do not make for success, either for the patient or doctor.

In the present state of knowledge and finance, it seems sensible to encourage regional centres with a special urodynamic interest. Many patients' bladder troubles can be solved perfectly satisfactorily with standard clinico-radiological approaches and simple dynamic tests like voiding urine flow rate. If not, the regional urodynamic team can be consulted, who will often want to carry out combined pressure-flow MCUs on such problem patients. Bladder symptoms may appear dreary, but they are the cause of much misery. We now have an established, exciting tool for doing research and offering help. We had better use it well.

Thomas Sherwood.

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1976, *British Journal of Radiology*, *49*, 979–995 DECEMBER 1976

Review article

Pancreatic scanning*

By J. E. Agnew, B.A., M.Sc., M. Maze, M.B., M.R.C.P., and C. J. Mitchell, B.Sc., M.B., M.R.C.P.

Department of Medical Physics and Academic Department of Medicine, Royal Free Hospital, Pond Street, London, N.W.3

(*Received April, 1976 and in revised form July, 1976*)

ABSTRACT

The ^{75}Se-selenomethionine pancreas scan cannot differentiate between chronic pancreatitis and carcinoma of the pancreas and may—although chiefly in certain defined clinical conditions—give a false-positive result. It is also rather more time-consuming than other radioisotopic scanning procedures. Its value in clinical practice stems from the fact that all the other methods currently available for studying the pancreas have their own disadvantages. Because a normal scan is only rarely seen in patients with carcinoma of the pancreas, pancreatic scanning can be particularly useful in helping to decide which patients should, and which should not, be subjected to other procedures involving greater discomfort or risk.

The value of pancreatic scanning as a diagnostic procedure remains debatable despite some 15 years of experience and the technique has undoubted shortcomings. This article reviews the current status of pancreatic scanning, particularly in the context of other available tests of pancreatic function, and considers the problems which still exist in interpretation of the abnormal scan.

METHODS

Radiopharmaceutical

Pancreatic scanning is founded upon the demonstration by Blau and Bender (1962) that a small but sufficient proportion of intravenously administered ^{75}Se-L-selenomethionine is taken up by the normal pancreas. Apart from the substitution of selenium for sulphur within the molecule, ^{75}Se-selenomethionine has the same molecular structure as the natural amino acid methionine—and similar biological properties. However as a radioactive tracer it has several disadvantages. The long physical half-life (120 days) and slow biological clearance severely limit the dose which may be given and in any case not more than 7% of the dose is taken up in the pancreas. Significant uptake in the liver and small bowel restricts pancreatic visualization. The complex γ-ray spectrum is not well suited to the gamma camera and complicates the choice of a second isotope for subtraction techniques.

Many alternative tracers have therefore been investigated. Ionic forms of zinc, manganese and caesium have all proved unsuccessful (Meschan *et al.*, 1959; Greenlaw *et al.*, 1962; Sodee, 1965; Cottrall and Taylor, 1970). Many amino acids are taken up well by the pancreas, but labelling with radioactive iodine totally alters their properties (Blau and Manske, 1961) and such compounds as iodinated tyrosine, tryptophan or phenylalanine have therefore proved unsuitable (Ullberg and Blomquist, 1968; Di-Giulio *et al.*, 1969; Varma *et al.*, 1969). The most attractive substitution label is perhaps ^{18}F as fluorinated compounds tend to be more stable *in vivo* than the corresponding iodinated compounds and the short half-life (110 minutes) should permit administration of high activities. However, clinical studies of ^{18}F-p-fluorophenylalanine and ^{18}F-fluorotryptophan have been disappointing (Cottrall *et al.*, 1973; Taylor and Cottrall, 1973) and fluorinated compounds may present a toxicity risk.

The poor results obtained with other substituted amino acids have led to further studies of ^{75}Se-labelled amino acids in an effort to achieve higher pancreatic uptake or faster biological clearance than ^{75}Se-selenomethionine. Two early failures were ^{75}Se-L-selenocystine and ^{75}Se-DL-mesoselenocystine which both failed to show significant pancreatic uptake (Melmed *et al.*, 1969). A recent multi-centre trial of six ^{75}Se-labelled amino acids has proved equally disappointing. An extract from the results is shown in Table I. Although several compounds had shorter biological half-lives than ^{75}Se-selenomethionine this was only due to rapid renal excretion of much of the dose. The only organs showing significant uptake were the liver and the kidneys (Tothill and Heading, 1975; Agnew and Maze, 1976).

Preparation for scanning

Amino acid metabolism in the pancreas is influenced by numerous dietetic or pharmacological factors which might therefore alter uptake of ^{75}Se-selenomethionine. Various preparatory régimes have

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This review is partly based on a paper presented at the Third Congress of the European Association of Radiology, Edinburgh, June, 1975.

*Copies of this review article may be obtained from The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG at a cost of 70p; remittance with order please.

TABLE I

Trial of ^{75}Se analogues of amino acids—results from three centres
(Pope and Ackery, 1975; Tothill and Heading, 1975; Agnew and Maze, 1976)

Agent	No. of patients	No. with possible visualization of pancreas
Se-(2-aminoethyl)-L-selenocysteine	14	2
Se-methyl-L-selenocysteine	7	1
Se-ethyl-L-selenocysteine	3	—
L-selenoethionine	10	2
D-selenomethionine	5	—
DL-α-amino-3-benzo(b)selenophenpropionic acid	4	—

been proposed; the more extreme claims made on behalf of some have been appropriately castigated by Bachrach *et al.* (1972). Our own experience is that starvation and anticholinergic therapy may have an adverse effect on pancreatic uptake while animal studies have confirmed that pre-treatment with probanthine significantly depresses pancreatic uptake (Winston *et al.*, 1974).

In a large series of patients reported by Creutzig *et al.* (1972) administration of pancreozymin prior to ^{75}Se-selenomethionine injection gave a significant improvement in pancreatic visualization. Similarly Winston *et al.* (1974) found that urecholine followed by pancreozymin led to an increase in the quality of the scan and a decrease in the proportion of falsely abnormal reports; the side effects of urecholine were reported to be well tolerated. Enhancement of uptake can only be of practical use if it improves the differentiation between normal and abnormal scans and some procedures might lessen this by increasing uptake in the abnormal pancreas. Pancreatic stimulation with pancreozymin could prove useful in studying pancreatic insufficiency secondary to interruption of the normal physiological pathways stimulating the pancreas.

Scanning technique

The pancreas occupies a deep and variable abdominal position; its axis is seldom parallel to the body surface. Generally the patient is scanned in a supine position with the detector anterior. Scanning in a postero-anterior projection is ruled out by absorption of γ rays in the vertebral column. The depth of the pancreas represents an unfavourable counting situation both in terms of the inverse square law and in terms of soft tissue absorption. Increases in its depth due to obesity, ascites or any large overlying mass can significantly reduce the count rate detected from all or part of the pancreas and can even cause total loss of the image—although the pancreas itself may be normal (Sodee, 1966; Agnew *et al.*, 1969; Agnew *et al.*, 1973). In addition the gamma camera has poor resolution at depth.

The shape of the normal pancreas is also variable and has been described as horizontal, pistol-shaped, transverse, sigmoid or, rarely, horseshoe-shaped (King *et al.*, 1966; Romanini and Troncone, 1968; Creutzig *et al.*, 1971). Several features characterize the normal scan (Fig. 1). There should be well marked uptake in the body and tail of the gland although there is frequently a thinning in the body; the lower margin of the head should present a well-defined convex border; bowel uptake is frequently seen adjacent to the tail of the gland (Melmed *et al.*, 1968). The thinning often seen in the body is due to compression of the pancreatic parenchyma by adjacent structures such as the spinal column, the abdominal aorta and the portal vein. Difficulties in determining the shape of the pancreas—particularly of the tail—may arise from confusion with uptake in the small bowel. However, overlap by the liver is even more important in interpreting the conventional pancreas scan. Attempts have been made to lessen this overlap by a variety of patient positions. Both hyperlordosis and elevation of the left side of the patient may help to separate the liver and pancreas images, particularly with the gamma camera (Possa *et al.*, 1967; Romanini and Troncone, 1968; Centi Colella *et al.*, 1972). These positions may not be so successful with the rectilinear scanner if they cause too great a displacement of the pancreas from the "focal plane" of the collimator (Steven *et al.*, 1969). In fact keeping the pancreas in that "focal plane" necessitates a collimator of long focal length with its front surface very close to the anterior body surface.

The count rate over the pancreas may continue to rise for two hours or longer after injection of ^{75}Se-selenomethionine (Goebel *et al.*, 1971; Centi Colella *et al.*, 1972; Goriya *et al.*, 1975). Despite this the optimum time for a rectilinear scan is shortly after

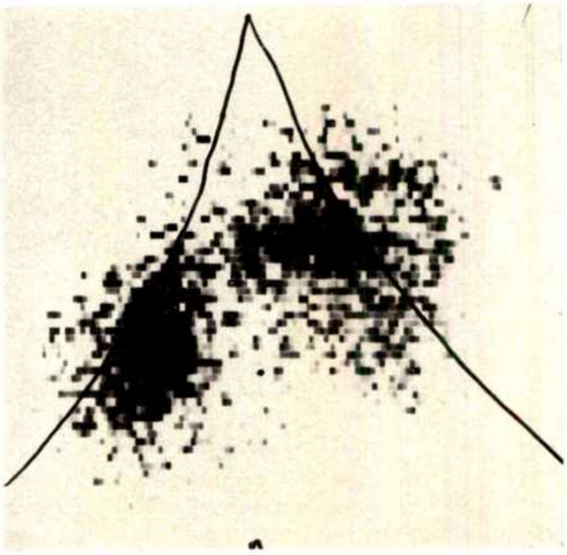

FIG. 1.

Normal pancreas scan showing well-defined uptake in head and tail of the pancreas with some bowel uptake. The thinning of uptake in the body of the pancreas is probably due to pressure from the adjacent expanded and tortuous aorta. (Shown by ultrasound and confirmed at surgery.)

administering the isotope because the ratio of pancreatic to background activity is generally highest some 30 minutes after injection. Blood radioactivity is then lowest (Charlesworth *et al.*, 1970a) whilst significant release of ^{75}Se radioactivity into the bowel contents does not occur until 60 to 90 minutes post injection (Youngs *et al.*, 1971). Serial views with a gamma camera have confirmed that the clearest pancreatic image is generally seen at 20 to 40 minutes (Landman *et al.*, 1971; Hatchette *et al.*, 1972).

A most important factor in obtaining a successful pancreas scan is the length of time taken. With a standard dose of 111 kBq (3 μCi) ^{75}Se-selenomethionine per kilogram body weight the count rate from the pancreas is inevitably low. For a 12.5 cm diameter crystal rectilinear scanner a scanning speed of the order of 24 cm/min is recommended (Agnew *et al.*, 1973). Similarly with the gamma camera, long exposures or serial views extending over at least 40 min have often been used (Bergeron and Vogel, 1970; Blanquet *et al.*, 1970; Landman *et al.*, 1971; Desgrez *et al.*, 1972; Hatchette *et al.*, 1972; Miale *et al.*, 1972).

Again, because of the low rate of gamma emission from the pancreas, some advantage can be gained from detecting both the principal peaks of the ^{75}Se spectrum. Experiments with a phantom have shown that in attempts to detect small defects (say 2–3 cm in diameter) the highest signal-to-noise ratio is obtained by using the output of two separate windows centred respectively on the 140 and 270 keV peaks (Steven *et al.*, 1969).

Subtraction scanning

Double isotope subtraction techniques are now in common use to eliminate the liver image from the ^{75}Se-selenomethionine scan. The second isotope must be taken up only in the liver. Colloidal preparations of ^{99}Tc^{m} and ^{198}Au have been frequently chosen. The former, because of its short half-life, permits the safe administration of high activities but its γ-ray emission (140 keV) coincides exactly with one of the principal peaks in the ^{75}Se spectrum. Subtraction of a ^{99}Tc^{m} or ^{198}Au liver image from the ^{75}Se image can be readily done when all the data is stored in digital form. Determination of the correct factor by which to multiply the liver-marker image prior to performing the subtraction may be done by a trial-and-error process or by considering the ratio of the count rates from the two isotopes within a "region of interest" centred over the right lobe of the liver. With a rectilinear scanner a relatively inexpensive analogue subtraction unit—similar to that first described by Kaplan *et al.* (1966)—can often produce an acceptable image (Fig. 2) but a recent comparative study has shown that digital methods are more reliable (Bergmann *et al.*, 1973).

No subtraction method can work for patients in whom the liver-marker isotope and the ^{75}Se-selenomethionine are not identically distributed. As the ^{75}Se is taken up by hepatocytes and colloidal ^{99}Tc^{m} or ^{198}Au by Kupffer cells, any disease causing differences in the relative distributions of these two types of cells can cause areas of apparent uptake not corresponding to the pancreas (Eaton *et al.*, 1967; Blanquet *et al.*, 1970). In addition, uptake of colloid in the bone marrow or of free ^{99}Tc^{m}-pertechnetate in the stomach can cause artefacts (Eaton *et al.*, 1967; McCready and Cottrall, 1971).

It is important to appreciate that the subtraction scan cannot have as good resolution as the conventional scan because the data processing performed inevitably degrades the image to some extent. Subtraction images can never be quantitatively exact due to statistical fluctuations and to differences in absorption of the two isotopes in varying thicknesses of liver tissue (Meckstroth and Staub, 1973) and, in addition, the ratio of ^{99}Tc^{m} to ^{75}Se counts over the liver has been shown to change significantly over the duration of a rectilinear scan (Charlesworth *et al.*, 1970b). No subtraction technique can cope with a massive thickness of overlying liver tissue which

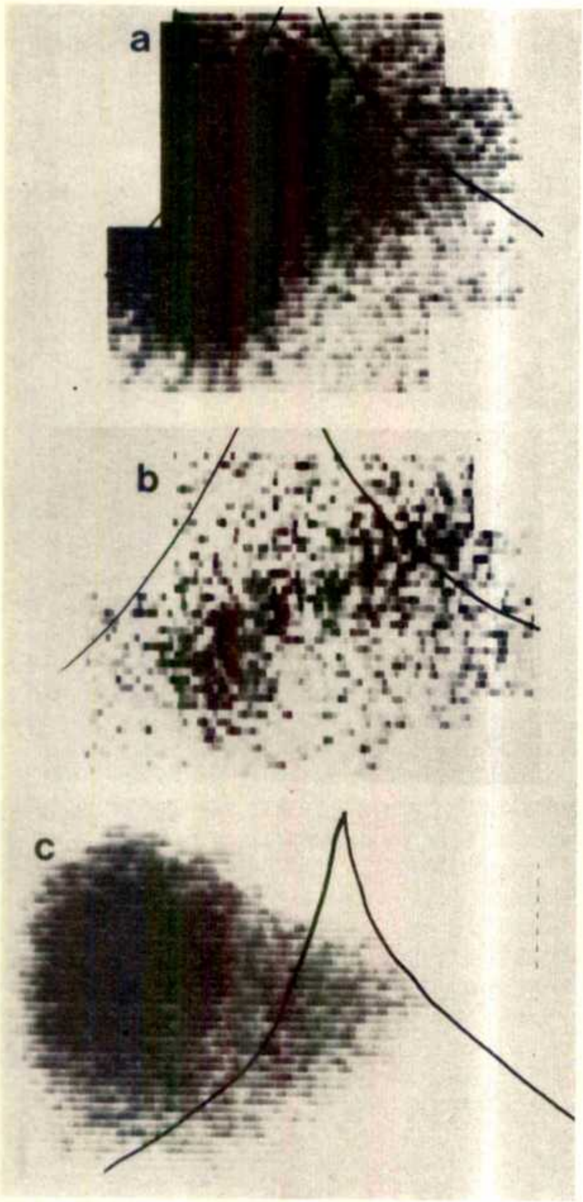

FIG. 2.

Typical sequence of scans: (a) conventional pancreas scan; (b) subtraction scan; and (c) liver scan. Body and tail of the pancreas are much more clearly shown in (b) than in (a).

interposes too much γ-ray absorbing material between pancreas and detector (Agnew *et al.*, 1973). If it is suspected that apparently poor uptake on a pancreatic subtraction scan may be due to this, ultrasonic scanning may be useful. This readily demonstrates the thickness of liver tissue in the overlap zone. If the overlapping liver is shown to be thin then a scan report of an abnormal pancreas can be issued with greater confidence.

Overlap of the pancreas image by uptake in the proximal gastrointestinal tract presents a more subtle problem. No simple scan, analogous to the liver scan, can be performed to indicate where the overlap problem may exist. Comparisons with duodenography have shown that the most common sites of isotope uptake in the bowel are the duodenal loop and the region of the duodenal-jejunal flexure—and that in some 12% of patients the jejunum lies in a position overlapping the body or tail of the pancreas (McCarthy *et al.*, 1969). An intestinal scan after oral administration of ^{99}Tc^{m}-pertechnetate may assist in differentiation between intestinal and pancreatic uptake and can be subtracted from the ^{75}Se-selenomethionine image (Henry *et al.*, 1973). There is, however, no quantitative basis for this subtraction as the distributions of the two isotopes in the intestine are not the same. The initial uptake of ^{75}Se-selenomethionine in the intestines is primarily intramucosal; only low levels are present in the intestinal contents for at least an hour (Youngs *et al.*, 1971).

Radiation dosimetry

A standard dose of 111 kBq (3 μCi) ^{75}Se-selenomethionine per kilogram body weight gives an absorbed dose to the pancreas of approximately 25 mGy (2.5 rad). The dose to the liver is about 50 mGy, to the kidneys 46 mGy, and to the gonads 20 mGy; the whole body dose is about 17 mGy (Lathrop *et al.*, 1972). To this must be added the dose from the liver-marker isotope. With ^{99}Tc^{m} sulphur colloid the activity administered is typically about 90 MBq (2.5 mCi) (McCready and Cottrall, 1971), giving some 9mGy to the liver and 0.5 mGy to the whole body (Atkins *et al.*, 1975). With ^{198}Au-gold colloid a typical activity is 5.5 MBq (150 μCi) (Agnew *et al.*, 1973), giving about 60 mGy to the liver and about 2 mGy to the whole body (Cloutier *et al.*, 1975).

THE CLINICAL ROLE OF THE PANCREAS SCAN

The potential value of a good pancreas scanning technique is high. Investigation by more conventional methods is time consuming and often yields equivocal results. But it has yet to be established whether pancreas scanning is of value as a specific diagnostic procedure or whether it should be regarded as a convenient method for screening patients with suspected pancreatic disease. For the latter purpose it has the advantages that it requires no preparation of the patient and can be performed on an out-patient basis, and that it is painless and safe.

It usually carries the additional bonus of a liver scan—frequently of advantage in patients referred for pancreatic investigation (McCready and Cottrall, 1971). The disadvantages are that the isotope is comparatively expensive, the procedure time-consuming, and interpretation sometimes difficult. From the clinical point of view some of the disillusionment with the results of the procedure is perhaps due to a failure to appreciate the indications for pancreas scanning and its limitations. All too often the pancreatic scan is clutched at as a final despairing diagnostic straw.

The possible causes of an abnormal scan include: acute pancreatitis, pancreatic pseudocyst, relapsing pancreatitis, chronic pancreatitis, pancreatic carcinoma, functioning tumour, and obstructive jaundice, but in addition an abnormal scan may arise from various causes other than exocrine pancreatic disease (see Table III).

In acute pancreatitis, absence of isotope uptake during the first week is well established (Blanquet *et al.*, 1970; Leger *et al.*, 1970; Spencer *et al.*, 1974). The value of scanning at this time is doubtful. The diagnosis is usually evident from simpler procedures and the scan appearance has no prognostic significance. It has become our policy to delay scanning until at least six weeks after the acute episode by which time the scan should be normal (Blanquet *et al.*, 1970; Leger *et al.*, 1970; Bouchier *et al.*, 1972; Desgrez *et al.*, 1972), and an abnormal scan suggests continuing pancreatic disease.

The scan appearance with pseudocyst formation has not in our experience proved diagnostic. Undoubtedly a pseudocyst can give a spectacular image of a well-defined localized region with no uptake (Prior and Valente, 1970; Desgrez *et al.*, 1972). Often however no defined lesion is seen and, if the cyst is extrapancreatic, it may completely escape detection (Blanquet *et al.*, 1970; Doutre, 1974). In rare instances the cyst may be in communication with the pancreatic duct giving the effect of a mass with positive uptake of isotope (Melmed *et al.*, 1968). A recent report has illustrated *delayed* accumulation of ^{75}Se in a cyst which was not visualized in the routine scan (Mattar and Prezio, 1975). Given this wide range of appearance it seems clear that ultrasonography is a far better test for a suspected pseudocyst (Leopold, 1972; Stuber *et al.*, 1972; Doust, 1975; Lutz *et al.*, 1975; Weill *et al.*, 1975b).

Appearances vary in relapsing pancreatitis from normal to complete absence of uptake—probably reflecting the varying degrees of pancreatic damage which have occurred. In chronic pancreatitis, the scan has been shown to reflect the degree of damage sustained. In 63 patients from whom pancreatic biopsies were obtained, Leger *et al.* (1971) reported excellent overall correlation between the degree of scan abnormality and independent histological assessment. In other studies, patients with severe damage as shown by steatorrhoea, glucose intolerance and greatly depressed duodenal trypsin levels always show marked impairment of isotope uptake (Agnew *et al.*, 1973). Calcification of the pancreas is almost invariably associated with abnormal scans (Prior and Valente, 1970; Quinton *et al.*, 1970; James *et al.*, 1974).

Normal scans are found in not more than 4% of patients with pancreatic carcinoma (McCarthy *et al.*, 1972). It must be stressed that this low false-negative rate applies to patients referred for scanning with symptoms suggesting pancreatic disease. Such symptoms only arise at a late stage in the course of pancreatic carcinoma and pancreas scanning would undoubtedly be far less successful if applied as a screening test for carcinoma in a population free from symptoms. Obviously the expense, duration and radiation dose of the procedure also make it quite unsuitable as a screening test in this sense. Small tumours, less than 2 cm in diameter, cannot be demonstrated by scanning unless they happen to block the pancreatic duct or are surrounded by more extensive inflammation. By far the most common scan abnormality seen in patients scanned with carcinoma of the pancreas is a loss of uptake throughout the pancreas.

The scan appearances with a functioning tumour are variable. Insulinomas are frequently small and are therefore often not detected (Steinhoff and Pabst, 1968; Centi Colella *et al.*, 1970; McCarthy *et al.*, 1972). A recent report has suggested that iodinated diphenylhydantoin may act as a specific agent for detection of insulinomas (Balachandran *et al.*, 1975). Functioning tumours associated with the Zollinger-Ellison syndrome may show enhanced isotope uptake in the tumour mass (Brown *et al.*, 1968; Melmed *et al.*, 1968; Agnew *et al.*, 1973) and metastases from such tumours may also show uptake (Thomas *et al.*, 1968; Staab *et al.*, 1971).

In obstructive jaundice, combined liver and pancreas scanning can be a considerable aid to the clinician in elucidating a diagnosis. A normal pancreas scan (Figs. 3 and 4) virtually excludes carcinoma of the pancreas as the cause of the obstruction (Doutre *et al.*, 1970; Heslip and Overton, 1971; Miale *et al.*, 1972; Agnew *et al.*, 1975). Inevitably, an abnormal scan is less helpful since abnormalities are found in a significant number of patients with

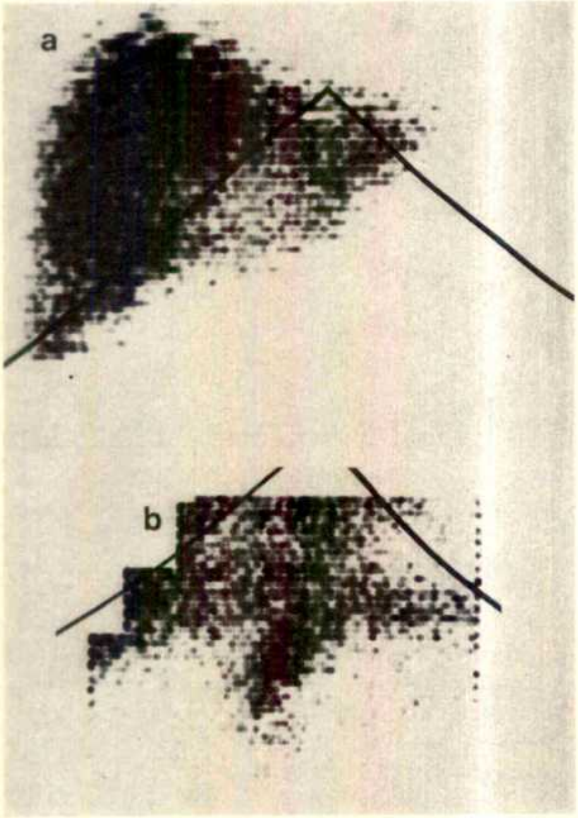

FIG. 3.

Obstructive jaundice due to carcinoma of the common hepatic duct: (a) liver scan with well defined hilar defect; (b) normal pancreas scan. Pancreas normal at operation.

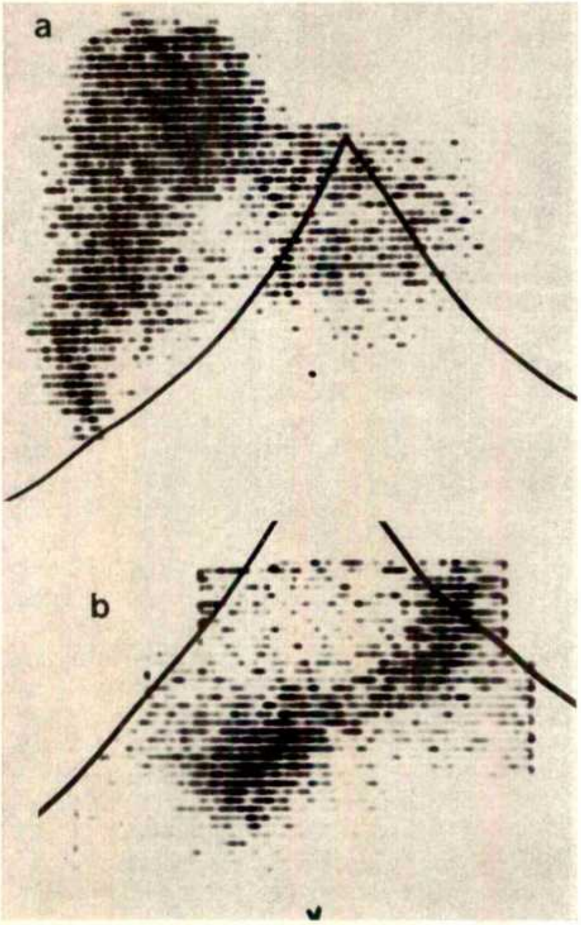

FIG. 4.

Obstructive jaundice due to a stone in the common bile duct: (a) liver scan showing enlarged liver with pronounced hilar defect; (b) normal pancreas scan. Pancreas normal at operation.

obstruction due to a bile duct carcinoma or to a stone in the common bile duct. Such abnormalities frequently reflect a pancreatitis caused by obstruction of the pancreatic duct at or near the ampulla of Vater. In pancreatic carcinoma causing obstructive jaundice we have found that 60% of scans show a severe loss of isotope uptake *throughout* the gland (Agnew *et al.*, 1975). In contrast, the incidence of severe generalized abnormality in carcinoma of the bile or hepatic ducts was 8%, and the majority of patients with tumours above the level of the cystic duct had normal scans.

Scan abnormalities in chronic pancreatitis and in carcinoma of the pancreas

The differentiation between chronic pancreatitis and carcinoma of the pancreas solely on the basis of the scan is a major problem (Eaton *et al.*, 1968; Fink *et al.*, 1969; Prior and Valente, 1970; Quinton *et al.*, 1970; Centi Colella *et al.*, 1972). It is clear from the many reports that the scan is rarely normal in either condition. But a wide variety of features, some of them contradictory, have been considered to favour one diagnosis rather than the other and the contradictions have been well reviewed elsewhere (Bachrach *et al.*, 1972). The particular feature which has most often been thought to favour a diagnosis of chronic pancreatitis rather than carcinoma of the pancreas is marked intestinal uptake of ^{75}Se-selenomethionine (Deininger, 1969; Blanquet *et al.*, 1970; Doutre *et al.*, 1970; Prior and Valente, 1970; Troncone *et al.*, 1970; Centi Colella *et al.*, 1972; Desgrez *et al.*, 1972). Delayed pancreatic uptake has also been reported to favour a diagnosis of chronic pancreatitis (Blanquet *et al.*, 1970; Quinton *et al.*, 1970; Troncone *et al.*, 1970), as has heterogeneous

TABLE II

FEATURES OF THE ABNORMAL PANCREAS SUBTRACTION SCAN—BLIND REPORTING RESULTS

Diagnosis	No. of patients	Severe generalized loss of uptake	Localized filling defect	Patchy uptake	Pancreatic outline preserved	Significant intestinal uptake	Pancreatic uptake apparently delayed*
Chronic pancreatitis	59	33	6	18	7	33	14
Carcinoma of pancreas	51	25	10	12	5	31	7

*Assessed by comparison of subtraction scan started about one hour after ^{75}Se-selenomethionine injection with conventional scan started 5–10 minutes post injection.

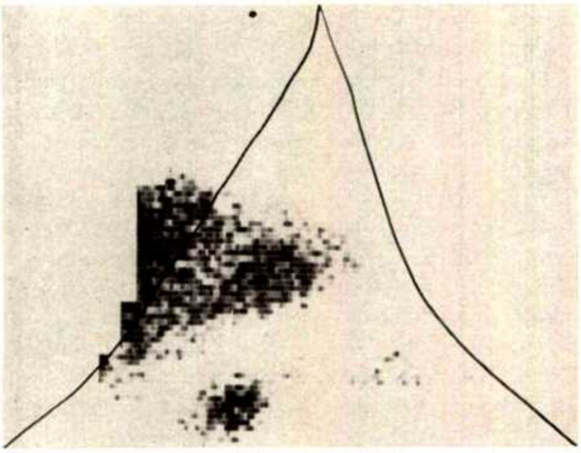

FIG. 5.

Conventional pancreas scan in chronic pancreatitis, showing marked loss of uptake in body and tail of the pancreas.

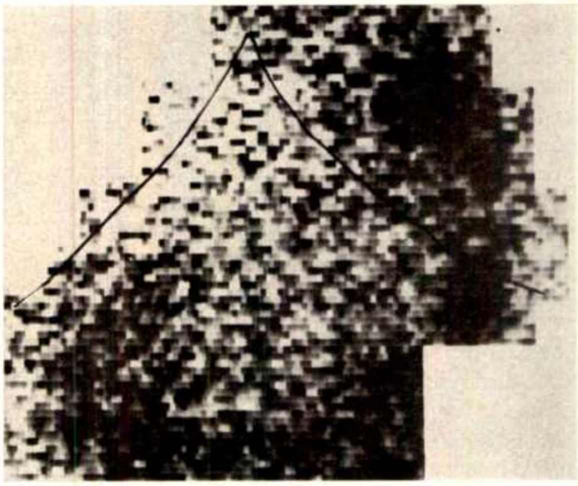

FIG. 6.

Subtraction pancreas scan in carcinoma of the pancreas, showing severe loss of uptake throughout pancreas together with marked bowel uptake.

or "patchy" uptake (Blanquet *et al.*, 1970). Preservation of the outline of the pancreatic image has been reported to be of some value in differentiating "mild" chronic pancreatitis from carcinoma (Centi Colella, 1975). Doutre (1974) has, however, pointed out that marked bowel uptake together with apparently heterogeneous pancreatic uptake may also be seen in patients who have undergone total pancreatectomy, and therefore casts doubt on the value of such "signs". We have recently put a range of the scan features claimed to contribute to differential diagnosis to a trial using blind marking techniques (Table II). Severe loss of uptake throughout the pancreas was common in both chronic pancreatitis and in carcinoma. Filling defects were reported in approximately 10% of patients with pancreatitis (Fig. 5) as against 20% of those with carcinoma, confirming that even the finding of a filling defect is of no definite diagnostic value. Significant bowel uptake proved to be as common in carcinoma (Fig. 6) as in pancreatitis. No discriminatory value could be attached to patchiness of uptake or preservation of the pancreatic outline. Although delayed pancreatic uptake was more common in pancreatitis than in carcinoma, the difference failed to reach either statistical significance or clinical utility. Our results re-emphasize that scanning alone is quite unable to differentiate between malignant and inflammatory disease.

Falsely abnormal scans

If inability to differentiate chronic pancreatitis from carcinoma is the major failing of the pancreas scan, the falsely abnormal scan must run it a close second as a reporting problem. False-positive rates of 15–30% have been reported in patients with no other evidence suggesting exocrine pancreatic disease (Liewendahl and Kvist, 1970; Rodriquez-Antunez *et al.*, 1970; Bender *et al.*, 1971; Hundeshagen *et al.*, 1971; Landman *et al.*, 1971; McCready and Cottrall, 1971) and even higher rates have been reported (Levrat *et al.*, 1970; Nundy *et al.*, 1974). Inevitably, however, pancreatic "normality" is difficult to define. An attractive proposition is to consider as "normal" only those patients in whom the pancreas has been inspected at laparotomy—although even this does not exclude the possibility of some dysfunction. Three series using the criterion of surgical normality have however found false-positive rates in the range 20–33% (Agnew *et al.*, 1973; Braganza *et al.*, 1973; Centi Colella, 1975).

In fact it is hardly surprising that this should occur. It has become clear that pancreatic uptake of ^{75}Se-selenomethionine depends on many extra-pancreatic factors. The acinar cells of the pancreas use methionine (or selenomethionine) in producing digestive enzymes and their requirement for methionine is related to the rate of pancreatic enzyme secretion. Among the factors which act on the acinar cells are vagal stimulation and gastrin, and indeed a recent review has stressed that "the whole length of the gut, from the body of the stomach to the colon, may affect pancreatic secretion by nervous or hormonal pathways" (Harper, 1975). The requirements for good uptake of ^{75}Se-selenomethionine in the pancreas include a functioning vagus nerve, normal gastric secretion, normal hepatic function, efficient pancreatic drainage and normal proximal gastrointestinal tract anatomy. Table III gives a list of conditions other than exocrine pancreatic disease in which an abnormal scan is likely.

Some 40 to 55% of patients with diabetes have abnormal scans (Espiritu and Rolfs, 1972; Spencer *et al.*, 1974) although abnormality is particularly likely in insulin-dependent diabetics (Lähdevirta, 1967; Melmed *et al.*, 1968). Techniques other than the scan will often have to be employed although the Lundh test may also be abnormal (Zeitlin and Sircus, 1974).

A similar situation arises in chronic liver disease. The pancreatic scan is frequently abnormal (Fink *et al.*, 1969; Agnew *et al.*, 1973) but intubation tests, particularly in patients with alcoholic liver disease, have indicated varying degrees of pancreatic dysfunction (Mezey *et al.*, 1970; Dreiling 1971; Roggin *et al.*, 1972). Peptic ulcer disease is associated with abnormal scans in 30 to 50% of patients (McCarthy, 1970; Quinton *et al.*, 1970; Espiritu and Rolfs, 1972). To some extent this may well reflect dysfunction of the pancreas. Impaired pancreatic secretion in response to secretin-pancreozymin stimulation has been reported in gastric ulceration despite normal pancreatic appearances at operation (Wormsley, 1972). Similarly, patients with a duodenal ulcer have shown subnormal response to varying doses of secretin (Berstad *et al.*, 1974).

TABLE III

Conditions associated with an abnormal scan in patients with no exocrine pancreatic disease

Well established	Also reported
Diabetes mellitus	Gastritis
Cirrhosis	Gastric carcinoma
Peptic ulceration	Inanition
Previous gastric surgery	Thyrotoxicosis
Ascites	Drugs (*e.g.* anti-cholinergic therapy)
Obesity	Naso-gastric suction

Patients who have previously undergone gastric surgery present an important clinical problem because often they return to hospital, perhaps some years later, with symptoms suggesting pancreatic insufficiency. Very frequently the scan is abnormal (Melmed *et al.*, 1968; Quinton *et al.*, 1970; Agnew *et al.*, 1973; Spencer *et al.*, 1974). Duodenal intubation tests have also indicated some tendency towards exocrine insufficiency in such patients (Zotti *et al.*, 1970; Dreiling, 1971; Malagelada *et al.*, 1974). Nevertheless the insufficiency indicated in this way is frequently far less severe than that suggested by the scan. It thus appears that ^{75}Se-selenomethionine uptake is readily affected by surgical disturbance of the normal pathways of pancreatic stimulation. The scan, except when it happens to be normal, is of no value to patients who have previously undergone gastric surgery; their pancreatic function should generally be investigated by other means.

Scan abnormalities due to ascites or obesity arise from the increased distance between the pancreas and the detector. The less frequent sources of an abnormal scan (Table III) have been discussed elsewhere (McCarthy *et al.*, 1972; Miale *et al.*, 1972); some, such as coincident nasogastric suction or the administration of anticholinergic drugs, are avoidable. Once allowance is made for the whole range of conditions causing pancreatic scan abnormalities (Table III) the false-positive rate in the remaining patients falls to a more acceptable level and a majority of the remaining "true" false-positive scans occur in patients with duodenal trypsin levels near the lower limit of normality (Agnew *et al.*, 1974). It is doubtful whether attempts should be made to reduce the level of false-positive reports further with the equipment and radiopharmaceuticals at present available. There is an inverse relationship between false-positive and false-negative scan reports. In the field of liver scanning it has been demonstrated that the overall error rate of individual reporters remains remarkably constant at about 20% and that the distribution of false-positive and false-negative reports varies within this overall rate (Ludbrook *et al.*, 1972). Undoubtedly a similar situation applies in pancreas scanning and any attempt to reduce false-positive results still further would imply a willingness to accept an increase in false-negative reports.

COMPARISON OF SCANNING WITH OTHER TECHNIQUES

Of the common biochemical tests, determination of serum amylase is helpful in acute pancreatitis. The detection of a sufficiently high level is diagnostic and an excellent reason for not proceeding immediately to a scan. However, serum amylase is only transiently elevated in the acute attack and not significantly elevated in chronic disease; serum lipase remains elevated for longer, but the estimation is more difficult. Glucose, xylose tolerance tests and faecal fat determinations do not provide information which is specific to the pancreas.

More specific information can be obtained by tests involving duodenal intubation. Direct tests of pancreatic function require complete collection of duodenal contents following stimulation of the pancreas either with secretin (Dreiling, 1975) or with a combination of secretin and pancreozymin (Burton *et al.*, 1960; Wormsley, 1972). Indirect tests are based on sampling duodenal contents after stimulation with a test meal, most commonly the Lundh meal (Lundh, 1962; James, 1973; Mottaleb *et al.*, 1973).

In distinguishing the abnormal from the normal pancreas, Dreiling (1975) has reported the accuracy of a standard secretin test to be approximately 90% in a series of more than 5000 cases with about equal proportions of false-positive and false-negative findings. Comparing scanning with the secretin-pancreozymin test, Braganza *et al.* (1973) found the intubation test considerably more accurate than the scan. This arose from the high false-positive rate of scanning—30% compared with 7% for the intubation test. The control group however included several patients with biliary disease, cirrhosis or diabetes. In patients with pancreatic pathology the false-negative rate of the secretin-pancreozymin test was slightly higher (12%) than that for scanning (9%). It is noteworthy that some 10% of patients had to be excluded from the study because the intubation test was incomplete or abandoned. The Lundh meal is easier to perform and less demanding on the patient (Waller, 1975). In patients with chronic pancreatitis or carcinoma the false-negative rate is high—in the region of 30%—but the false-positive rate in normal patients is very low (Mottaleb *et al.*, 1973; Youngs *et al.*, 1973). The Lundh test can therefore play a useful role in conjunction with the scan. If performed simultaneously the measurement of duodenal radioactivity may be substituted for enzyme estimation. The concentration of ^{75}Se in duodenal aspirate 90–120 min after ^{75}Se-selenomethionine injection correlates well with the trypsin concentration and can be easily and rapidly measured (Youngs *et al.*, 1971). In contrast, simultaneous performance of the secretin-pancreozymin test and the scan works less well. In particular it tends to give a high proportion of false-positive scans (Nundy *et al.*, 1974); one possible reason for this is that the nasogastric suction required tends to have an adverse effect on selenomethionine uptake. The Lundh test does not demand nasogastric suction and there is no evidence that intermittent sampling of duodenal contents has any effect on selenomethionine uptake. The combination of a normal Lundh test and an abnormal scan suggests that the scan may be falsely positive whereas if both tests are abnormal there is a very high probability that pancreatic pathology exists (Youngs *et al.*, 1973).

Intubation tests, like the scan, are unable to distinguish between neoplastic and inflammatory disease. Unlike the scan they are of very little value in lesions affecting only the tail of the gland (Dreiling, 1975). Patients with scans correctly showing filling defects in the body or tail of the pancreas but with functioning tissue in the head usually give a normal intubation test (Youngs *et al.*, 1973). It is the patients with a generalized scan abnormality but a normal intubation test in whom the pancreas is eventually likely to be found normal.

Few major studies have yet attempted to assess the role of scanning relative to that of pancreatic radiology. The comparison is complicated by the range of available radiological techniques and by the variety of findings indicative of disease (Eaton *et al.*, 1972).

The value of a simple abdominal X ray in revealing pancreatic calcification is widely appreciated. Calcification is especially prevalent in alcoholic chronic pancreatitis (Sarles and Gerolami-Santandrea, 1972; Bernades *et al.*, 1975) but is a less common feature of pancreatitis in countries where alcohol is not the predominant aetiological factor (James *et al.*, 1974). Although calcification can be found in conditions other than chronic pancreatitis (Minagi and Margolin, 1972), its rarity in carcinoma of the pancreas is diagnostically important (Guien, 1972).

Significant abnormalities in a barium meal and follow-through examination occur in pancreatic disease but many cases of carcinoma fail to be detected (Bouchier, 1970; Rösch, 1975). Abnormalities of the duodenal loop are better seen with hypotonic duodenography (Raia and Kreel, 1966; Kreel, 1969; Stage and Banke, 1969; Shirley, 1974). The method is however unsuitable for lesions of the body and tail and has a false-negative rate of about 20% in carcinoma of the head (Ferrucci and Eaton, 1973). In contrast the false-positive rate is low; of 46 patients with no pancreatic disease studied by Shirley (1974) only one had a hypotonic duodenogram falsely suggesting carcinoma.

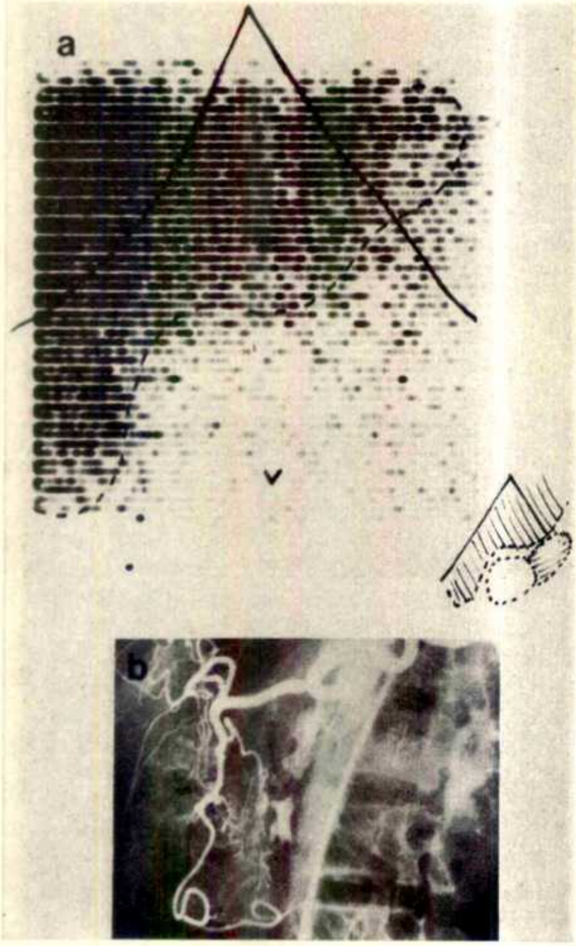

FIG. 7.

Carcinoma of the pancreas: (a) scan showing severe loss of uptake in the head of the pancreas with moderate loss in the body and tail; and (b) arterial phase of angiogram showing increased vascularity plus truncation of an arterial branch in the region of the head of the pancreas.

Several reports have attributed to pancreatic angiography (Figs. 7b and 8c) a very high error rate (Nebesar and Pollard, 1967; Eaton *et al.*, 1968; Fredens *et al.*, 1969), and an interesting series is that of Bookstein *et al.* (1969) who on *prospective* reporting found a false-negative rate of 24% in pancreatic carcinoma. Kreel (1972) has commented that the angiographic signs of pancreatic carcinoma are "difficult to see and elicit". Sometimes abnormality may only be detected in the venous phase and then perhaps only from the displacement of adjacent vessels (Fig. 8). The technique is clearly demanding but some studies have shown that a high degree of accuracy can be achieved (Boijsen and Tylen, 1972; Buranasiri and Baum, 1972; Rösch, 1975).

Recently the introduction of endoscopic retrograde pancreatography (ERP) has made possible direct visualization of the pancreatic ducts (Blumgart, 1975; Salmon, 1975). We are at present comparing the relative value of scanning and ERP (Mitchell *et al.*, 1976). There was complete agreement on 35 of 41 patients (85%) in which a laparotomy or autopsy diagnosis was available (Table IV). One carcinoma was missed by scanning and two by ERP. The most important distinction between the two investigations lies in the extent to which ERP, if successful, can indicate the site and nature of the pathology (Figs. 8, 9 and 10). The extent to which ERP can pinpoint the site and magnitude of an obstruction to the pancreatic duct is demonstrated in Fig. 8b; both scanning (Fig. 8a) and angiographic (Fig. 8c) findings in this patient were far less clear or specific. Demonstration of the dilated duct system characteristic of chronic pancreatitis (Fig. 10b) likewise provides information which cannot be obtained from the scan (Fig. 10a). Many reports have agreed that a normal scan in a patient with symptoms suggesting pancreatic disease makes it unlikely that the patient's symptoms result from a pancreatic carcinoma. A completely *normal* scan should therefore be seen as a result which precludes the necessity for the more hazardous and invasive ERP.

The diagnostic potential of computerized X-ray axial tomography (Hounsfield, 1973) in pancreatic investigation cannot yet be assessed. The pancreas shows considerably less absorption than neighbouring organs but absorption in malignant tissue does not appear to differ significantly from that in normal tissue (Alfidi *et al.*, 1975a). The effect of disease on pancreatic morphology can therefore be demonstrated (Alfidi *et al.*, 1975b) but the discriminatory

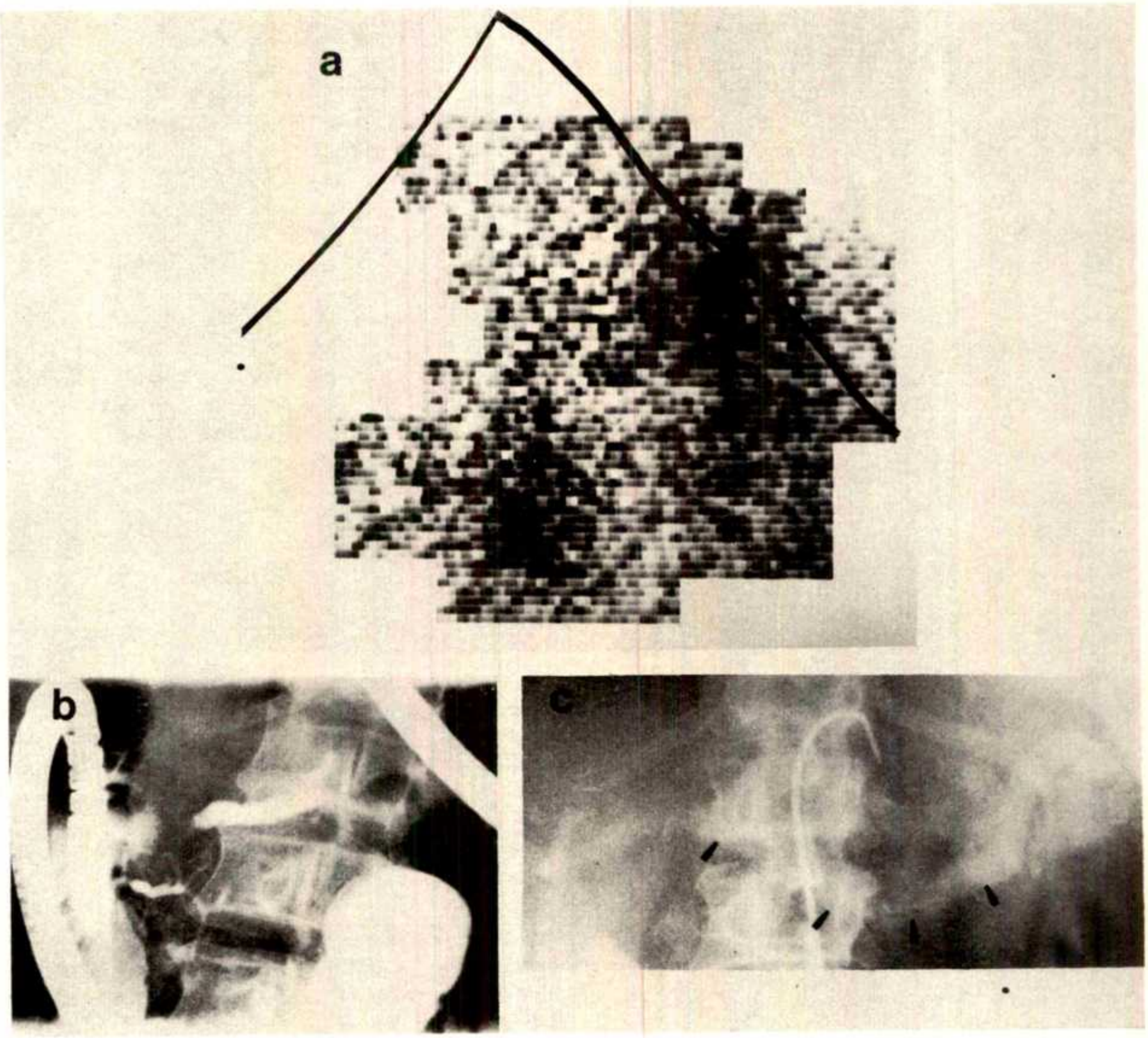

FIG. 8.

Carcinoma of the pancreas: (a) scan showing moderate loss of uptake with pancreatic displacement; (b) ERP showing a stricture in the head of the pancreas with distal dilation of the duct; (c) venous phase of angiogram showing displacement and irregularity of the splenic vein (arrowed).

TABLE IV

COMPARISON OF SCANNING AND ENDOSCOPIC RETROGRADE PANCREATOGRAPHY IN PATIENTS WITH OPERATIVELY PROVEN DIAGNOSES

	Normal	Chronic pancreatitis	Carcinoma of pancreas
Normal scan, normal ERP	12	—	—
Abnormal scan, normal ERP	2	1	2
Normal scan, abnormal ERP	—	—	1
Abnormal scan, abnormal ERP	1	10	12
Total	15	11	15

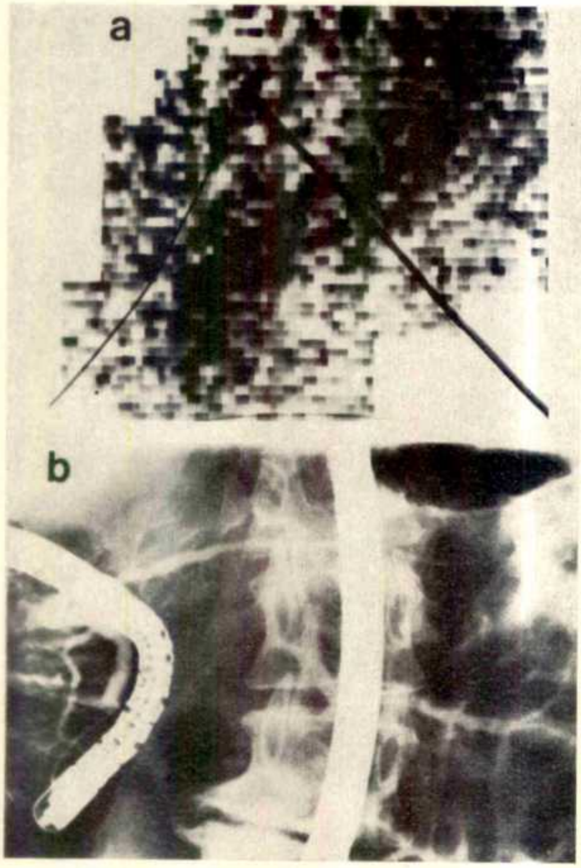

Fig. 9.

Almost complete recovery after single attack of acute pancreatitis: (a) scan showing mild loss of uptake; (b) ERP showing normal duct system.

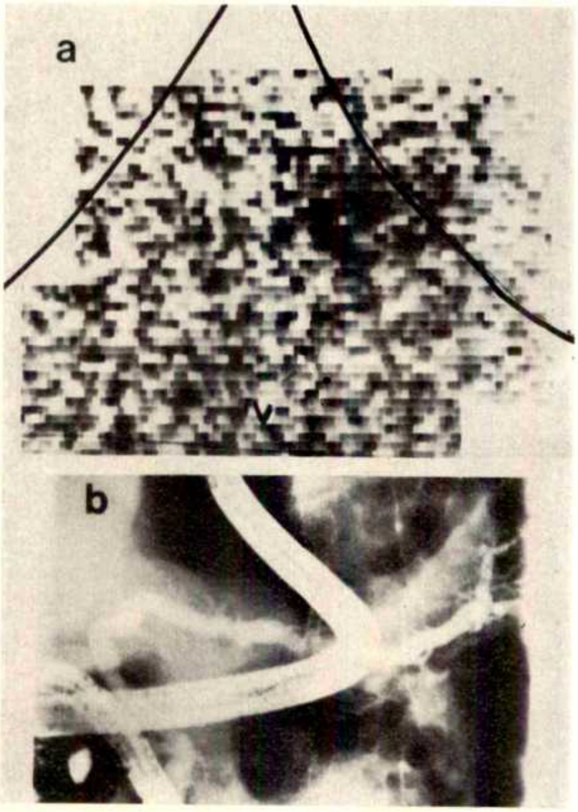

Fig. 10.

Chronic pancreatitis: (a) scan showing severe generalized loss of uptake; and (b) ERP showing a markedly dilated main pancreatic duct with dilation of the secondary radicles.

value of such information remains to be established.

Ultrasonic scanning is now proving increasingly successful in diagnosing pancreatic disease and is of proven value in the detection of pseudocysts. Encouraging results in differentiating neoplastic from inflammatory disease of the pancreas have recently been reported (Lutz *et al.*, 1975; Walls *et al.*, 1975; Weill *et al.*, 1975a, 1975b). In one series, 19 of 26 carcinomas were correctly diagnosed with a false-positive rate in normal subjects of 21% (Walls *et al.*, 1975).

Future Developments

It is evident that at present no single test can both adequately assess pancreatic function and provide specific diagnosis of disease. Several groups have therefore suggested the use of combinations of tests performed simultaneously. A recent example includes measurement of bicarbonate, enzyme and radioselenium secretion into the duodenum, cytology of the duodenal aspirate, hypotonic duodenography and scanning. This combined approach was almost totally successful in distinguishing patients with established pancreatic disease from those without (Nundy *et al.*, 1974). Such combined studies require carefully planned co-ordination between different hospital services. In centres where combined testing is considered impracticable, we consider it is important that clinicians should adopt the most effective sequence of tests. The choice of tests for any particular patient will depend on the provisional diagnosis (Eaton *et al.*, 1968; Bouchier, 1970). One scheme for an effective *sequence* of tests has been proposed by Ferrucci and Eaton (1973) and we, like these authors, feel that the selenomethionine scan can contribute as an initial diagnostic step once the clinical suspicion of pancreatic disease has arisen. A normal scan almost rules out pancreatic disease and may preclude the necessity of proceeding to more hazardous or uncomfortable tests.

As sophisticated grey scale equipment for ultrasound becomes more widely available, ultrasound too is likely to prove valuable as an initial investigation. We believe that radioisotope scanning and ultrasound should be regarded as complementary. A major problem in performing ultrasonic scanning is deciding the probable position of the pancreas (Burger and Blauenstein, 1974; Weill *et al.*, 1974). In many cases a prior radioisotope scan will identify the position of the pancreas and thus facilitate both performance and analysis of the ultrasound scan. Where the radioisotope scan suggests disease, ultrasound may often be able to identify its nature.

Computer-based techniques are already well established for subtraction scanning of the pancreas, particularly in conjunction with the gamma camera. Measurement of uptake in different zones of the pancreas can contribute to differentiating the normal from the abnormal scan (Agnew *et al.*, 1969) and can be most accurately done by computerized "region of interest" techniques. Already these have been elegantly applied in demonstrating pancreozymin enhancement of ^{75}Se-selenomethionine uptake (Creutzig *et al.*, 1972). Dynamic pancreas studies using a computer–gamma camera link may help to differentiate patients with mild pancreatitis from those with malignant disease (Centi Colella, 1972), and the technique has obvious value as a research tool in, for instance, studying the rate at which pancreatic radioactivity decreases after pancreozymin and secretin stimulation (Goriya *et al.*, 1975). Nevertheless we are doubtful whether such techniques are likely to prove of great clinical value.

Conspicuously the greatest need within the radioisotope field is for a better radiopharmaceutical. Research continues into methods of enhancing pancreatic uptake of ^{75}Se-selenomethionine (Lewander, 1975) but it seems unlikely that any enhancement procedure can totally transform the present nature of pancreas scanning. New agents labelled with ^{18}F, ^{75}Se and ^{131}I have all proved disappointing. Possibly, however—for centres close to a cyclotron—the advent of agents labelled with ^{11}C (Vaalburg *et al.*, 1975; Comar *et al.*, 1976) may constitute a breakthrough.

CONCLUSIONS

The practical value of pancreatic scanning becomes much more acceptable if several considerations are taken into account. There is a high probability that a normal scan indicates a normal pancreas. Being a convenient and safe investigation suitable for out-patients, scanning is therefore certainly of value as an initial investigative test. It must be accepted at present that the scan will not provide a pathological diagnosis, and an effective specific tumour-localizing agent for pancreatic carcinoma is needed. In common with other currently available techniques, scanning cannot provide *early* detection of carcinoma.

The problem of false-positive scans has rightly been emphasized by many workers. However, when the known causes of a false-positive scan are excluded, the "true" false-positive rate falls to an acceptable level. Even in patients with diseases likely to produce a falsely abnormal scan, the investigation can still be of help as a normal scan will be of significant benefit to clinician and patient. When the scan is abnormal, a higher proportion of patients will require further investigation only to reach the eventual conclusion that the pancreas is probably normal.

In comparison with ideal criteria for a diagnostic test, pancreatic scanning has marked deficiencies. But in relationship to other currently available diagnostic methods pancreatic scanning stands up well.

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Lumbar myelography with metrizamide – a new non-ionic contrast medium

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ABSTRACT

In contradistinction to all currently available water-soluble contrast media, metrizamide (Amipaque) is not a salt, but a substituted amide and therefore does not dissociate in solution. This unique property results in solutions of high iodine content yet with low osmolality. Metrizamide probably has a lower neurotoxicity than any other known water-soluble contrast agent.

A clinical trial of metrizamide lumbar myelography in 201 patients in three clinical centres represents the first clinical assessment of this new contrast medium in the United Kingdom. The technique of the radiological procedure and the adverse reactions encountered are presented and discussed.

There were no serious adverse effects: no muscle spasm or epilepsy. Minor adverse reactions—headache, vomiting and nausea occur with approximately the same frequency as with meglumine iocarmate: 43% of patients complained of headache.

In 118 patients, the lower dorsal subarachnoid space was also examined with no increase in toxic reactions.

It is concluded that metrizamide is a safe contrast medium for lumbar and lower dorsal myelography. Water-soluble media will probably largely replace oil products for these investigations.

Further clinical trials are being extended to include examination of the upper dorsal and cervical subarachnoid space.

This paper reports the first clinical trial in English-speaking countries of a contrast medium of original chemical structure with unique chemical and physical properties.

Contrast media at present available for myelography fall short of optimal requirements (Grainger, 1975). For adequate demonstration of the subarachnoid space and its delicate extensions into the nerve root sheaths, the contrast medium must opacify the cerebro-spinal fluid (CSF) itself: it must therefore be water-soluble so that it is fully miscible with CSF. It must have radio-opacity sufficient to demonstrate the spinal cord and nerve roots without being so radio-opaque as to obscure detail. The contrast medium must have a low systemic toxicity and low neurotoxicity; it must not irritate the meninges to an inflammatory response (either acute or chronic), and it must be completely eliminated from both the subarachnoid space and the body within a few hours.

No currently available contrast medium approaches these criteria and this has led to considerable controversy among neuroradiologists throughout the world.

In the U.K., U.S.A. and other English-speaking countries, water-soluble contrast media were not used until four or five years ago because the only such medium then available was methiodal sodium (Abrodil) which was so irritant that its injection had to be preceded by spinal anaesthesia, and its use restricted to the subarachnoid space below the conus medullaris. It had considerable neurotoxicity and poor radio-opacity. In the English-speaking countries, an oil-soluble iodinated contrast medium—iophendylate (Myodil, Pantopaque)—was used virtually exclusively, for it is painless to inject, does not cause immediate arachnoid or neurological irritation and can be used throughout the spinal subarachnoid space. Its disadvantages are however considerable. The rate of absorption from the subarachnoid space is very slow and variable, but usually about 1 ml per year. As much as possible should therefore be removed following the study, but its removal is often the most unpleasant part of the procedure and is often incomplete. The protein bound iodine plasma level is elevated, often for several years: this interferes with tests of thyroid function and could be associated with thyroid dysfunction. Iophendylate is not miscible with CSF and therefore cannot penetrate into the delicate nerve root sheaths, so that some disc lesions with nerve root compression cannot be demonstrated. Iophendylate is an irritant to the meninges, leading to chronic arachnoiditis which in some patients may be severe and symptomatic.

In Norway and many other European countries, the disadvantages of iophendylate are considered to be so significant that this medium is rarely used. The

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Swedish health authorities prohibit the use of iophendylate in the subarachnoid space. For demonstration of the lumbo-sacral nerve roots, methiodal was used, preceded by spinal anaesthesia. For examination of the spinal cord, gas myelography was used, requiring tomography on a tilting table because of the poor radiographic contrast.

This controversial situation remained unchanged for more than 30 years until 1970/71 when a new contrast medium—meglumine iocarmate (Dimer X)—was developed specifically for myelography. The introduction of meglumine iocarmate converted many radiologists to water-soluble myelography, for it produces excellent radiographic visualization of the lumbo-sacral nerves and their root sleeves. This contrast medium has however an appreciable neurotoxicity and with few exceptions, most investigators restrict examination to the conus medullaris and the lumbo-sacral nerve roots. Only a few investigators (notably de-Villiers (1974) in Pretoria, South Africa) use meglumine iocarmate for myelography of the dorsal and cervical regions.

The present report concerns the use of a completely new water-soluble contrast medium—metrizamide (Amipaque)—synthesized by Nyegaard & Co., Oslo according to an original proposal by Almén (1969). Its unique chemical, physical and toxicological properties suggest that this product could be utilized safely for myelography of the entire spinal subarachnoid space.

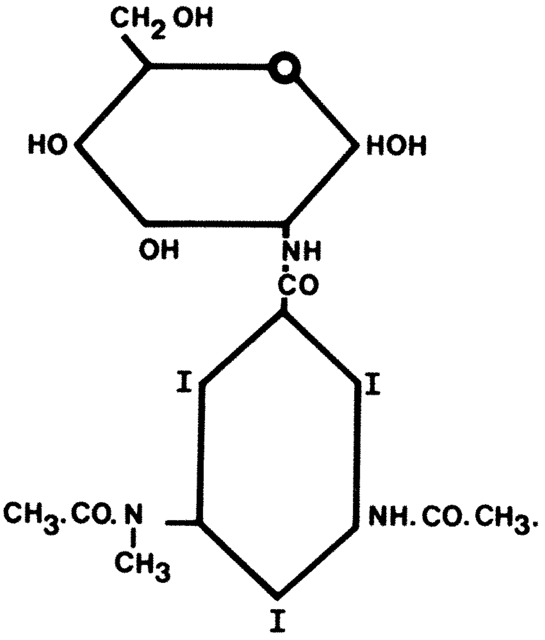

FIG. 1.

Metrizamide 2-(3-Acetamido-5-N-Methylacetamido-2,4,6-Triodobenzamido)-2-Deoxy-D-Glucose.

Metrizamide was subjected to its first clinical assessment for lumbar myelography in 1972 in a four centre trial in Oslo (×2), Stockholm and Brussels (*Acta Radiologica Supplement No. 335* (1973)).

THE CONTRAST MEDIUM

Metrizamide is a water-soluble tri-iodinated contrast medium which, unlike previous such contrast media, is *non-ionic* and therefore does not dissociate in solution. Its solutions therefore have a much lower osmolality than conventional ionizing water-soluble contrast media, all of which are salts.

Its chemical name is 2-(3-acetamido-5-N-methyl acetamido - 2,4,6 - tri-iodobenzamido) - 2 deoxy - D - glucose and its chemical structure is that of a substituted amide (*not* a salt) and is illustrated in Fig. 1. It has a molecular weight of 789.1 and contains 42% w/w iodine. Metrizamide is supplied as a lyophilized powder which is dissolved by the investigator in a bicarbonate buffer solution (5 mg sodium bicarbonate/100 ml).

Metrizamide solutions have such low osmolality that a solution isotonic with CSF (or plasma) contains the very appreciable amount of 166 mg iodine per ml. Most of the investigations reported in this paper have been performed using isotonic solution of metrizamide, *i.e.* 0.300 osmols/kg and containing 166–170 mg iodine per ml.

The osmolality and iodine content of different water-soluble contrast media utilized for myelography are presented in Table 1.

TECHNIQUE

Preparation of the contrast medium

Vials containing freeze-dried metrizamide are supplied in two sizes containing 3.75 g and 6.75 g of

TABLE I

OSMOLALITIES OF WATER-SOLUBLE CONTRAST MEDIA SUITABLE FOR MYELOGRAPHY

	Concentration iodine mg/ml	Osmolality water mols/kg
Human blood or CSF		0.301
Metrizamide (Amipaque)	166	0.300
Metrizamide (Amipaque)	280	0.456
Meglumine iocarmate (Dimer X)	280	1.040
Meglumine iothalamate (Conray 280)	280	1.570
Methiodal sodium (Abrodil)	104	1.570

the powder. The manufacturers supply a chart indicating the volume of solvent (a very dilute buffered solution of sodium bicarbonate) to be added to achieve the desired concentration of metrizamide. For example, for an isotonic solution (170 mg iodine/ml), 8.9 ml of solvent is added to the 3.75 g vial, and 16.1 ml of solvent is added to the 6.75 g vial. The contrast medium should not be diluted with CSF. The solvent is injected by syringe through the rubber diaphragm of the vial. Solution is more speedily effected if air is excluded but five minutes with gentle agitation should be allowed for complete solution. Surplus solution should be discarded.

Preparation of the patient

In the great majority of patients, no premedication was used. In ten (out of 201 patients), diazepam was given as a pre-operative sedative.

Local anaesthesia was used in some patients for the lumbar puncture, but in the majority of patients no local anaesthetic or pre-medication was used.

Spinal anaesthesia is strongly contra-indicated.

Injection of the contrast medium

The lumbar puncture is performed with a fine needle (22 s.w.g.). The patient may be seated on the fluoroscopic table, or he may lie in lateral decubitus with the head end of the table elevated 20–30 deg. It is sometimes an advantage to fluoroscope during the injection of the contrast medium, for an extra 2–5 ml may be required to produce optimal results in patients with an unusually capacious lumbo-sacral subarachnoid sac. Fluoroscopy is more easily performed with the patient in the lateral decubitus position, with the needle connected by a fine polythene tube to the syringe.

Radiographic technique

After the introduction of contrast medium, the patient is placed prone on the fluoroscopy table, care being taken to ensure that the head is always well elevated above the lumbar region.

Radiography using the undercouch tube is generally satisfactory, but there are definite advantages in utilizing additional views with the patient in the lateral decubitus using a horizontal beam cross-table technique, when the dependent nerve root sleeves are well demonstrated.

The patient is maintained with the legs sufficiently dependent to keep the contrast medium in the lower lumbar region during the time taken to process and check the initial radiographs for radiographic quality and technique. Further radiographs are taken in the prone A.P., 15–30 deg. prone obliques, lateral decubitus horizontal ray and cross-table horizontal ray prone positions as required. The couch is then brought to the horizontal for demonstration of the upper lumbar levels. For demonstration of the conus medullaris, it may be necessary to move the contrast as high as the 8th dorsal vertebra. If the dorsal cord is being examined, the contrast medium column is best manipulated by turning the patient on to his *side* and *slowly* tilting the table 10–20 deg. head down under fluoroscopic control. The prone position is not advised for running the contrast medium towards the head, as the lumbar lordosis and the dorsal kyphosis do not permit the slow controlled movement of the contrast medium column which is essential. The lateral decubitus position is preferred: minimal movement of the patient, very slow table tilt under fluoroscopic control and flexion of the head towards the uppermost shoulder are essential technical points.

Lateral, P.A. supine, A.P. prone and lateral decubitus films are taken if the dorsal subarachnoid space is being examined. Once the contrast medium has reached the dorsal region, progressive dilution occurs and it becomes more difficult to obtain adequate films subsequently because of the progressive loss of radiographic contrast. If the cervical region is to be examined, then the contrast medium should be run into the cervical region first, before the lumbar and dorsal regions are examined. Alternatively, the contrast medium may be injected suboccipitally or by a lateral cervical approach.

The patient must be encouraged to move as *gently* as possible so as to maintain the contrast medium column and prevent unnecessary dilution.

As in all water-soluble myelographic techniques, the radiographic factors chosen should not exceed 75 or 80 kV, utilizing high mA and short exposures.

Post examination care

The patient should remain in bed for 24 hours, the head of the bed being elevated 15 deg. for the first six hours. A few patients in the series underwent surgery shortly after the examination: no problems were encountered.

THE PATIENTS

A series of 201 patients was investigated up to December 31, 1975 by the three authors at The Royal Hospital and Fulwood Annexe, Sheffield (R.G.G.) (65 cases), The Middlesex Hospital and National Hospital for Nervous Diseases, London (B.K.) (61 cases) and The London Hospital (I.G.W.) (75 cases).

TABLE II

ADVERSE REACTIONS FOLLOWING MYELOGRAPHY WITH METRIZAMIDE

Symptom	Severe degree	Moderate degree	Mild degree	Patients	%	Comments
Headache	16*	20	50	86	43	*One of these patients had pre-existing migraine
Nausea	2	19	7	28	14	
Vomiting	3	20	1	24	12	
Dizziness		7	2	9	4	†During the investigation when lying prone
Increased leg pain	1†	10	8	19	9	
Pain in neck and/or in back		6	2	8	4	‡Headache, stiff neck, stiffness in lumbar region and legs. Probably true meningism
Neck stiffness		2	2	4	2	
Meningism		1‡		1		
Leg symptoms		1§		1		§Lost feeling in both legs for a moment, then a tingling sensation
Insomnia		1		1		
Hallucinations		1		1		
Hyperacusis		1		1		
Vaso-vagal attack		1		1		

Total number of patients 201. Lumbar (201) including lower dorsal (118)

There were 124 males and 77 females. The age of the patients ranged from 11 to 76 years with an average of 44 years. A proforma sheet was completed for each patient.

The lumbo-sacral subarachnoid space was examined in all 201 patients. In 118 of these patients, the lower dorsal subarachnoid space was also examined.

THE CONTRAST MEDIUM

The average amount of iodine injected was 2195 mg, corresponding to 13 ml of solution containing 170 mg I/ml, *i.e.* a solution isotonic with CSF and blood.

The concentrations used varied from 160 mg I/ml to 230 mg I/ml and the volumes injected varied from 3 to 18 ml. In most cases, isotonic contrast medium solution was used—170 mg I/ml in 10–15 ml volume.

The lowest dose employed was 4 ml 160 mg I/ml and the highest 18 ml 170 mg I/ml.

RESULTS

Quality of radiographic demonstration of anatomical features

Good	85%
Fair	14%
Poor	1%

The less than satisfactory results usually stem from an under-estimation of the concentration or volume of contrast medium necessary, *e.g.* in patients with a capacious lumbo-sacral sac. This problem is reduced if fluoroscopy is used during the injection. Some patients made exaggerated responses when asked to move gently from one position to the next, and this tends to spread the contrast medium and reduce its radio-opacity.

TABLE III

FREQUENCY OF THE MOST COMMON SYMPTOMS AFTER LUMBAR AND LOWER THORACIC MYELOGRAPHY WITH METRIZAMIDE IN 201 PATIENTS, 124 MALES AND 77 FEMALES

	Total 201		Males 124		Females 77	
Symptom	Patients	%	Patients	%	Patients	%
Headache	86	43	50	40	36	47
Nausea	28	14	15	12	13	17
Vomiting	24	12	9	7	15	19

Metrizamide myelography (*U.K. December 1975*)
Lumbar (201) including lower dorsal (118)

Adverse reaction

All adverse reactions were recorded on a proforma sheet completed for each patient. The results are presented in Table II.

There were no major neurological complications.

Headache was by far the most frequent and significant adverse reaction (43%), being more severe and more frequently accompanied by nausea and vomiting in females (Table III).

There were no untoward cardiovascular complications, no significant hypotensive episode except in one patient who had a vaso-vagal attack.

Pulse and blood-pressure recordings were taken one or two hourly from before the procedure until six hours after the injection. There were a few patients who had significant rises in these parameters but these were all recorded immediately before or after the lumbar puncture, and were almost certainly due to apprehension.

Discussion

Technique

When a water-soluble contrast medium like metrizamide is injected with the lumbar theca maintained 30 deg. or more dependent, the contrast medium forms a radio-opaque layer below the cerebrospinal fluid, with relatively little mixing during the first few minutes. Thus, this technique usually provides a very adequate degree of radiographic contrast within the lower lumbar and sacral subarachnoid space, and within the lumbo-sacral nerve root sheaths. The very slender cavities of the nerve root sheaths are well outlined because the surface tension and the ease of flow of the contrast medium is similar to CSF with which it is miscible. On the other hand, the oil droplets of iophendylate have very different rheological properties to CSF and are not miscible with it: they therefore cannot adequately demonstrate the nerve root sheaths.

If the spinal canal is known to be narrow from a study of the plain films, it may be an advantage to use a more concentrated solution of metrizamide, especially in large patients. The capacity of the lumbar subarachnoid sac cannot be assessed on conventional radiographs and therefore we prefer to fluoroscope during the injection of contrast medium, and add an extra 3–5 ml if the subarachnoid space is unusually capacious. This fluoroscopic technique is, however, not essential.

Adverse reactions

It is important to differentiate the adverse reactions due to the contrast medium from that due to the technique of the lumbar puncture (Tourtelotte *et al.*, 1964). A few patients are very nervous and perspire despite reassurance, and the occasional patient may actually lose consciousness for a moment as the theca is punctured. In this series of 201 patients, two patients lost consciousness for a moment and had a short grand mal attack *before* the injection of metrizamide.

The low incidence of severe adverse reactions following injection of metrizamide encountered in the present series agrees with the findings of others (Skalpe and Amundsen, 1975; Hindmarsh, 1975; Hansen *et al.*, 1976). The incidence of uncomfortable minor side reactions has *not* been found to be less than after lumbar myelography performed with meglumine iocarmate.

(1) *Headache*

In our series, 43% (86 out of 201) patients experienced headache, which was severe in 16. In three patients the headache was very severe lasting more than two to four days.

Gonsette (to be published) reported 51% (28 out of 55) patients developed headache after lumbar myelography with metrizamide; Hansen *et al.* (1976) reported 43% (128 out of 300) patients similarly affected. Skalpe and Amundsen (1975) reported that 33% (200 out of 600) patients developed headache, usually minor but occasionaly severe and lasting a few days. Sortland *et al.* (in press) reported 15% of headaches for metrizamide lumbar myelography, increasing to 24% for thoracic and 45% for cervical myelography in 206 patients.

Lumbar myelography with meglumine iocarmate (Dimer X) was associated with headache in 20% of 3336 patients reported by Baumgartner *et al.* (1971) and 20% of 2000 patients reported by Grainger (1975). Both of these two studies involved multi-centre trials so that reporting may not have been uniform.

There have been few fully controlled double-blind trials of metrizamide and meglumine iocarmate lumbar myelography. In one such carefully controlled trial involving 43 patients in each group, Hindmarsh (1975) found 21% of patients developed headache in each group: the iocarmate patients seemed to have a more prolonged headache. Irstam and Sellden (in press) in another controlled trial involving 50 patients in each group found that 32% of the metrizamide group, and 38% of the iocarmate developed headache.

There would thus seem to be little difference in the incidence of headache following metrizamide or iocarmate lumbar myelography—probably 30–40% is a reasonable concensus.

Headache following metrizamide and iocarmate lumbar myelography is usually mild and lasts less than 24 hours. It is more frequent in females than males (Table III), Ahlgren (1975), Skalpe and Amundsen (1975); worse on sitting up and eased by lying down. These features are also found in the headache which frequently (?30%) follows simple lumbar puncture (Tourtelotte *et al.*, 1964) and is probably due mainly to escape of CSF through the puncture hole in the theca. It is therefore advisable to use a small gauge needle (*e.g.* 22 s.w.g.) and to posture the patient lying down with the head of the bed raised only 20 deg. after the myelogram. Sitting the patient up is now not necessary following lumbar myelography with metrizamide or iocarmate and will probably aggravate the headache.

In three patients in our series of 201, the headache was severe, lasted two to four days and was accompanied by nausea and vomiting. The reason for these severe reactions is not known. They may occasionally occur after simple lumbar puncture, but it is probable that the contrast medium itself is at least partially responsible.

(2) *Nausea and vomiting*

Nausea and vomiting occurred in 14% and 12% of the 201 patients respectively. These symptoms were almost always delayed until several hours after the myelogram and although sometimes repeated, were never severe. They were usually accompanied by headache and were more frequent and more marked in females (Table III).

(3) *Neurotoxic effects*

The great advantage of metrizamide over all other water-soluble contrast agents is its relatively slight direct neurotoxic effect (Gonsette, 1973). This is probably at least partially related to the low osmolality of metrizamide solutions (Table I). There is also probably a lower intrinsic chemical toxicity of this novel chemical compound. This low neurotoxicity allows a greater amount of metrizamide (than iocarmate) to be injected into the subarachnoid space.

As in previous studies, there was complete absence of any myoclonic jerking or epileptic fit in our patients. The only possible neuro-excitatory phenomena observed were hyperacusis in one patient, and minor transient hallucinations in another.

Since lesions as high as mid-dorsal can occasionally produce syndromes similar to those arising from lumbar lesions, a satisfactory contrast agent should allow the dorsal region to be studied when an adequate examination of the lumbar theca fails to explain the clinical picture. For these reasons, metrizamide would appear to be the contrast medium of choice for water-soluble myelography. Meglumine iocarmate has been used for dorsal and cervical myelography (de Villiers, 1974) but it is more liable to cause myoclonus than is metrizamide.

It is now recommended that no routine pre- or post-myelographic anti-epileptic medication be administered. If the patient receives undiluted contrast medium over the surface of the brain, then it is probably advisable to inject a long acting anti-epileptic drug such as phenobarbitone as a prophylactic against convulsions. Should spasm or convulsions occur following injection of metrizamide (or meglumine iocarmate) into the ventricles or subarachnoid space, then intravenous diazepem should be administered, repeatedly if necessary.

Transient EEG abnormalities occur in 16% of patients receiving intrathecal (lumbar) metrizamide (Kaada, 1973), probably related to the rapid passage of the contrast medium from the lumbar to the cerebral region (see later).

None of our patients developed epilepsy after metrizamide myelography. There have, however, been seven patients reported among 6000 in the clinical trial programme who developed one or more epileptic fit; six patients had cervical myelography. Hindmarsh *et al.* (1975), Nielsen (1975) and Sortland *et al.* (1975) each reported a single case of grand mal epilepsy, after the passage of metrizamide over the cerebral cortex. Hindmarsh *et al.* (1975) attributed the epilepsy in his patient to a lowering of the epileptogenic threshold by prior administration of a phenothiazine derivative (chlorpromazine), and neuroleptic drugs should be avoided.

Arachnoiditis

There was increase in lumbar and sciatic pain in 12% of our patients, most having only transient discomfort, probably due in part to the lumbar puncture and to the movement and posturing necessary during the myelogram which was usually performed without analgesia. There may however be a direct (but unproven) irritative effect of the contrast medium on the compressed nerve root and the meninges.

Transient increase in cell count, but not of the protein content occurs in the CSF in the 24 hours following metrizamide myelography (Hindmarsh, 1975)

Few of our patients have had repeated myelographic studies so that the possible occurrence of adhesive arachnoiditis cannot be assessed in our material. Adhesive arachnoiditis (which produces characteristic radiological changes) has been reported after spinal anaesthesia, laminectomy, myelography with iophendylate, methiodol, meglumine iothalamate and meglumine iocarmate (Skalpe, 1975; Ahlgren, 1973; Irstam *et al.*, 1974). Adhesive arachnoiditis has been shown to be related to the hyperosmolality of the contrast medium (Slatis *et al.*, 1974) and therefore it is only to be expected that meglumine iocarmate and metrizamide—the low osmolality contrast media—will produce less arachnoiditis than other contrast agents.

In a cumulative analysis from many different centres, 138 patients have had a repeat water-soluble myelogram after a previous metrizamide myelogram (Nyegaard, 1976b). Only one of these patients was shown to have developed arachnoiditis (and he also had disc surgery), so that it appears that metrizamide is less likely to cause arachnoiditis than any other known water-soluble contrast medium.

Elimination of metrizamide

Metrizamide is absorbed partly by the lumbar theca but probably principally through the parasagittal arachnoid granulations within the skull, perhaps dependent on the posture assumed after myelography. Greitz and Hindmarsh (1974) and others, utilizing the very sensitive computerized axial tomograph (EMI scanner), have demonstrated metrizamide in the basal cisterns of the skull and within the Sylvian fissures as early as three hours after lumbar injection. Metrizamide can be detected in the blood as early as 15 minutes after lumbar subarachnoid injection and reaches its maximum serum level in two hours (Golman, 1975). Seventy percent of the injected dose is excreted unchanged in the urine during the first 24 hours after lumbar injection (Golman, 1975). There are no metabolites of metrizamide detected on thin layer chromatography (Golman, 1975).

Rapid transport of metrizamide into the skull is probably responsible for the EEG changes and the very rare epileptic fit which has been reported after metrizamide myelography. EMI scanning studies after Dimer X (Danziger and Bloch, 1976) suggests similar dynamics after iocarmate lumbar myelography.

It is possible to drain some of the contrast medium following metrizamide myelography, but the absence of major side effects makes this probably unnecessary unless unusually large doses are used.

Diagnostic accuracy of water-soluble myelography

Almost all of our 201 patients were investigated for prolapsed lumbar intervertebral disc. Many of these patients have not yet had surgery. We have not yet analysed the diagnostic accuracy of myelography in this series, but we know of no case in which the operation did not confirm the myelographic finding.

Hirsch *et al.* (1969) recorded 91% diagnostic accuracy in 489 patients who were operated upon after methiodal lumbar myelography for lumbar disc lesions. Ahlgren (1969) and Praestholm and Lester (1970) found 96% and 97% correlation in 99 and 78 cases respectively in patients operated upon after iothalamate (Conray) lumbar myelography.

Hansen *et al.* (1976) confirmed the myelographic diagnosis in 94% of 193 patients operated upon after metrizamide lumbar myelography.

It is evident therefore that the diagnostic accuracy of water-soluble myelography (whatever the actual contrast medium) for lumbar disc prolapse is very high; well over 90% of patients operated upon prove to have the lesion identified on the myelogram. This is a higher percentage of diagnostic accuracy than can be obtained with oil myelography. In addition, a significantly greater number of nerve root compressions will be shown by water-soluble myelography than by oil myelography, for the water-soluble examination demonstrates the lumbo-sacral nerve roots and their sheaths in far greater detail than when oil is used.

CONCLUSION

The exceptional tolerance of metrizamide, the high diagnostic quality of the radiographs and the simplicity of the procedure combine to make metrizamide myelography a safe, simple and accurate procedure which is a much more pleasant experience for the patient than oil myelography combined with subsequent aspiration of the contrast medium.

We have been so impressed with lumbar and lower dorsal myelography with metrizamide and its low neurotoxicity, that we are now extending our examinations to include the cervical region.

ACKNOWLEDGMENTS

We wish to record our grateful thanks to Nyegaard & Co. A/S, Post Box 4220, Torshov, Oslo 4, Norway, the manufacturers of metrizamide (trade name Amipaque) for allowing us the opportunity of utilizing this new product and for the generous supplies of contrast medium. In particular, Mrs. Kamilla Dahlstrøm, Mrs. Lovice Hol and Dr. Torstein Renaa of Nyegaard & Co. A/S have been most helpful in this project.

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Computer tomography of traumatic extracerebral lesions

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ABSTRACT

Twenty-one traumatic intracranial extracerebral lesions in 15 patients were examined with the EMI scanner using the 160×160 matrix. The results were compared with operation and angiographic findings. Although angiography seems to be a more reliable diagnostic aid, computer tomography has important advantages as it provides information on the nature and extent of the extracerebral lesion as well as on concomitant brain damage.

As previously shown (Levander *et al.*, 1975) diagnosis of traumatic extracerebral lesions by computer tomography is somewhat more difficult than that of intracerebral haematoma. This has also been found by other authors (New *et al.*, 1974; Davis and Pressman, 1974; Paxton and Ambrose, 1974; Scott *et al.*, 1974; Baker *et al.*, 1975). Ambrose *et al.*, 1975 and Kramer *et al.*, 1975 have shown that the use of contrast media did not increase the diagnostic accuracy in these cases since no enhancement was obtained.

The aim of the present study was to study retrospectively extracerebral lesions and their appearance at computer tomography using the 160×160 matrix, and to compare these with the findings at cerebral angiography and operation.

PATIENTS AND METHODS

The study comprised 15 patients with extracerebral, intracranial, traumatic lesions examined with the EMI scanner, using the 160×160 matrix, between April and October 1975 at the Department of Neuroradiology, Karolinska Hospital, Stockholm. Only patients examined with computer tomography in between the trauma and operation or angiography were included.

In six patients both extracerebral and intracerebral lesions were found and five had more than one extracerebral lesion; these occurred at different occasions in one patient. The material comprised altogether 21 extracerebral lesions in the 15 patients (Table I). Seventeen lesions were operated upon and six of these were studied also by angiography. Three were investigated by angiography only and one was diagnosed by computer tomography only.

TABLE I

DETAILS OF 21 LESIONS IN 15 PATIENTS. PATIENTS ARE REFERRED TO IN THE TEXT BY THEIR CODE NUMBERS

Pat. Code No.	Attenuation	Diagnosis	Localization
1525	increased	epidural	left frontal
1588	increased	epidural	occ bilateral
,,	increased	subdural	right frontal
,,	increased	epi + sub	left temporal
1615	increased	subdural	right frontal
,,	decreased	hygroma	bilateral frontal
1630	increased	subdural	left frontal
1654	increased	epi + sub	temp. par, occ right
,,	increased	?	left parietal
1684	increased	epidural	left parietal
1733	increased	subdural	left par + temp
1268	decreased	subdural	left frontal
,,	not visible	?	right parietal
1368	decreased	hygroma	left frontal
,,	not visible	epidural	right frontal
1599	decreased	subdural	left frontal
1629	decreased	subdural	left fr + par
1471	mixed	subdural	right parietal
1612	mixed	subdural	right fr + par
1413	not visible	subdural	left temporal
1652	not visible	subdural	left parietal

Of the 21 lesions, 11 were subdural haematomas, one of which was not operated but considered by angiography to be a chronic subdural haematoma (1599). Four lesions were epidural haematomas and two were combined epi- and subdural haematomas. Two lesions were hygromas and two were not given a final diagnosis. One of the latter lesions was not operated upon but was verified by angiography (1268) which showed a typical avascular area. The other was a small extracerebral lesion which was not examined with angiography nor operated upon (1654 parietal) (Table II).

The findings at computer tomography were scrutinized from the following aspects: (1) the presence or absence of visible lesions; (2) the degree of attenuation in the visible lesions compared to that of the brain; (3) the depth of the lesions as calculated from the computer tomograms and compared with the dimensions on the angiographic films reduced by the magnification factor 1.2. At operation the depth was only occasionally measured with a ruler and was usually estimated by the neurosurgeon; (4) dislocation of the ventricles was recorded at computer tomography and displacement of the mid-line structures at angiography.

TABLE II

DISTRIBUTION OF THE DIAGNOSES AND THEIR MODE OF VERIFICATION

Diagnosis	No. of lesions	Verifications angio + op	op only	angio only
Subdural	11	4	6	1
Epidural	4	2	2	
Subdural + Epidural	2		2	
Hygroma	2		1	1
Unknown	2*			1
	21*	6	11	3

* One of the patients with unknown diagnosis was neither operated upon nor angiographically examined.

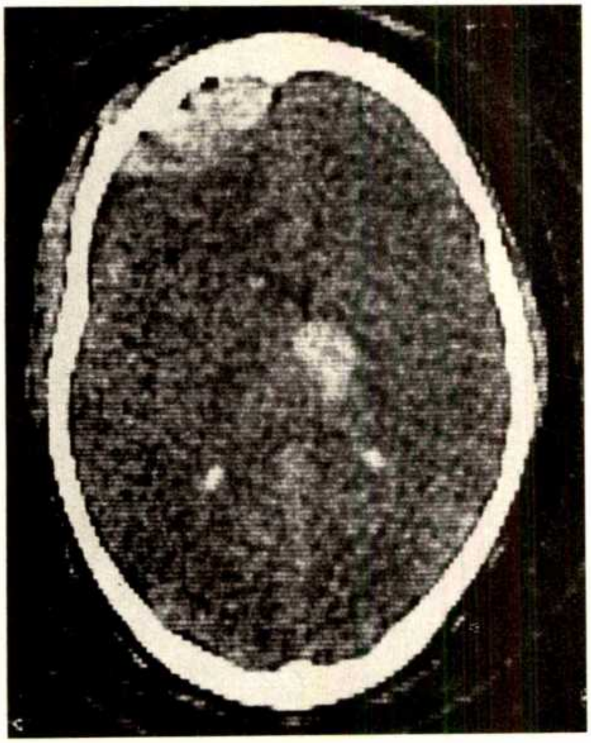


FIG. 1.

Patient No. 1525. Biconvex-shaped epidural haematoma on left side frontally. Coagulated at operation. Centrally on the right side an intracerebral haematoma which may have been prior to the trauma (see Levander *et al.*, 1973).

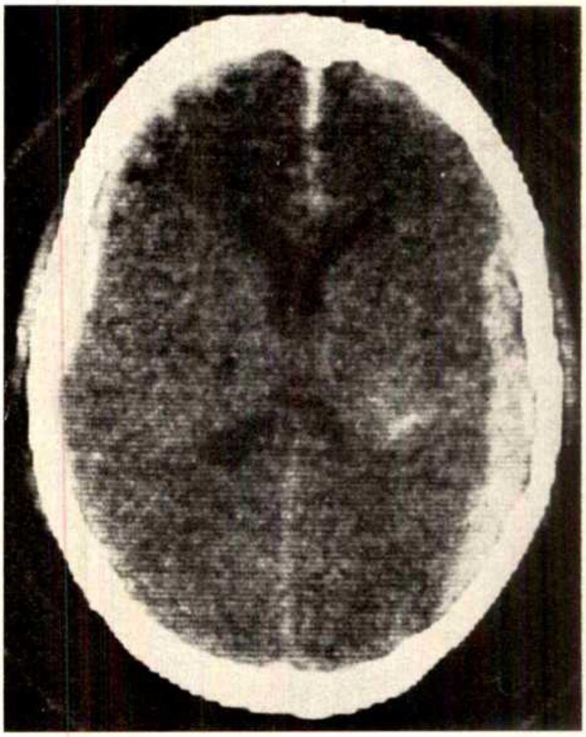


FIG. 2.

Patient No. 1654. Combined epi- and subdural haematoma on right side verified at operation. Displacement of the ventricles to the left. On the left side a narrow lesion with increased attenuation. This lesion was not verified by operation or angiography.

RESULTS

The lesions were divided into four groups according to their degree of attenuation; *increased attenuation* compared with that of the brain was found in ten lesions and in seven different patients (Fig. 1). Nine of these were verified at operation, one was not operated upon (Fig. 2) and was seen at computer tomography to be 5 mm thick. In one patient (1733) the time of the head injury was somewhat uncertain but the patient was admitted to hospital with fracture of the skull two days before computer tomography was carried out. Operation was carried out the same day as computer tomography and revealed a subdural haematoma with liquid contents as well as numerous blood clots (Fig. 3). The remaining eight lesions operated upon all contained solid blood clots. All patients had suffered head injuries on the day of or one–two days before computer tomography and operation. Only one patient had as long an interval between the head injury and computer tomography as five days.

Reduced attenuation was found in five lesions. Two of these were hygromas (1615, 1368) and the time of injury was uncertain. One hygroma was verified at operation (Fig. 4) and the other (1615), was considered to be a hygroma on the basis of clinical, angiographic and computer tomographic findings. This patient sustained a subdural haematoma two months later

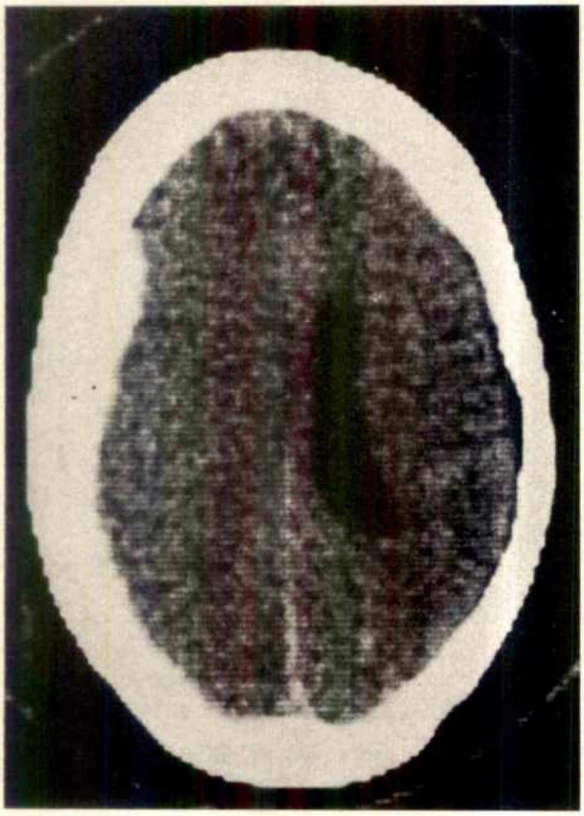
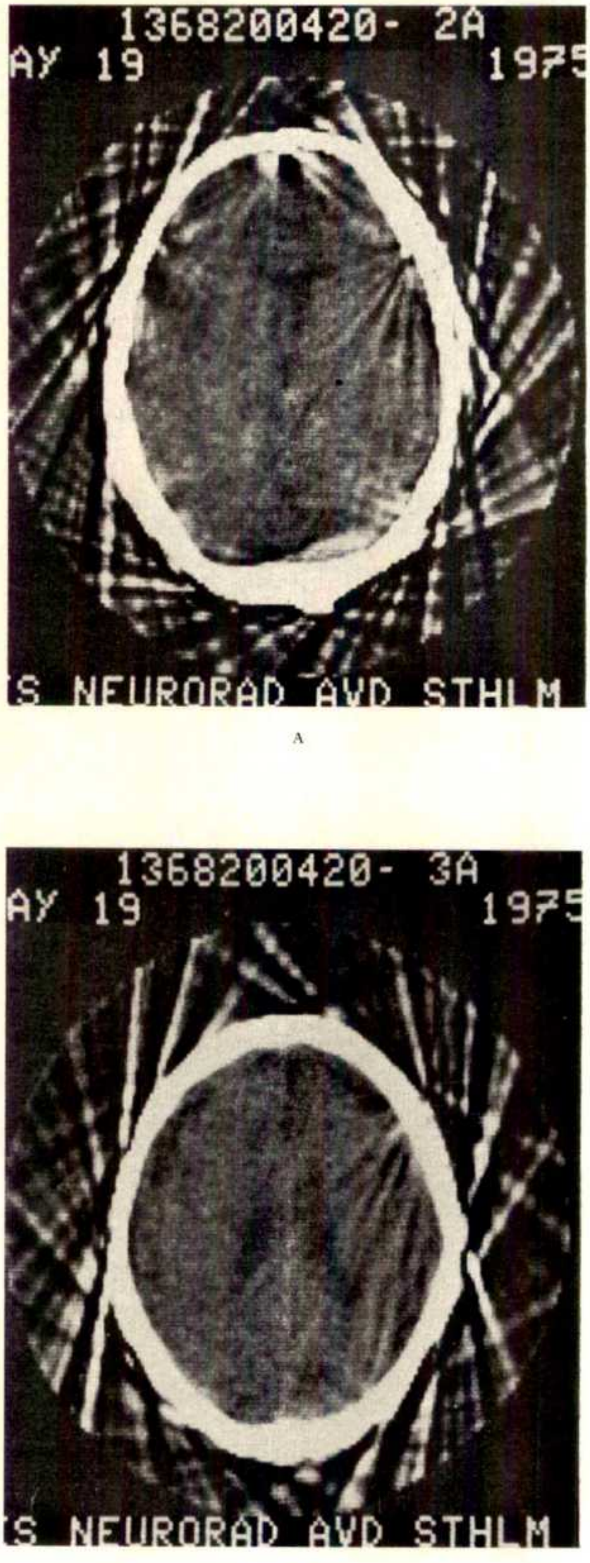


FIG. 3.

Patient No. 1733. Left-sided subdural haematoma containing liquid blood and blood clots at operation.

and was operated upon at that time (Fig. 5). A third patient (1599), injured more than three months before computer tomography, was not operated upon and angiography revealed a biconvex, chronic subdural haematoma. The remaining two patients (1268, 1629) were injured ten days before computer tomography. At operation both were found to have liquefied haematomas.

Mixed attenuation was found in two patients, each with one lesion (1471, 1612) (Fig. 6). Increased attenuation was found in the dependent part of the lesion in both instances. Liquefied contents and

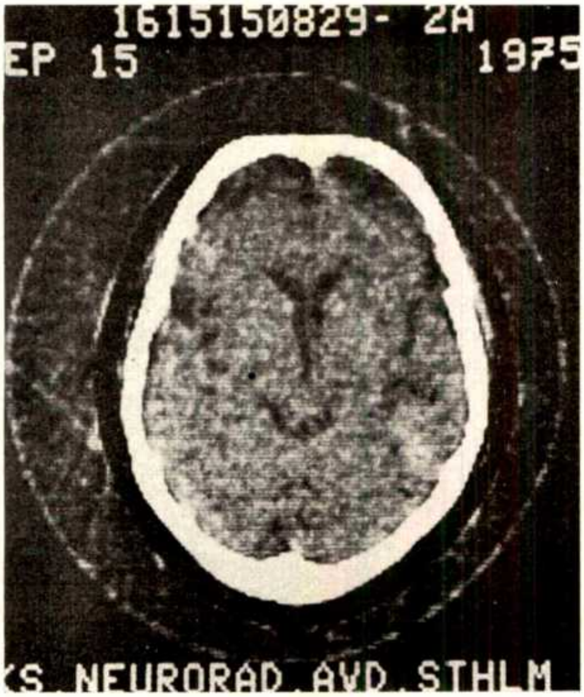


A

B

FIG. 4.

Patient No. 1368. Hygroma on the left side verified at operation, displacing the lateral ventricles backwards and to the right anteriorly. In the right frontal area artefacts originating from a fracture of the skull may be seen. A 4 mm thick, three-day-old epidural haematoma adjacent to the fracture is, however, not visible.



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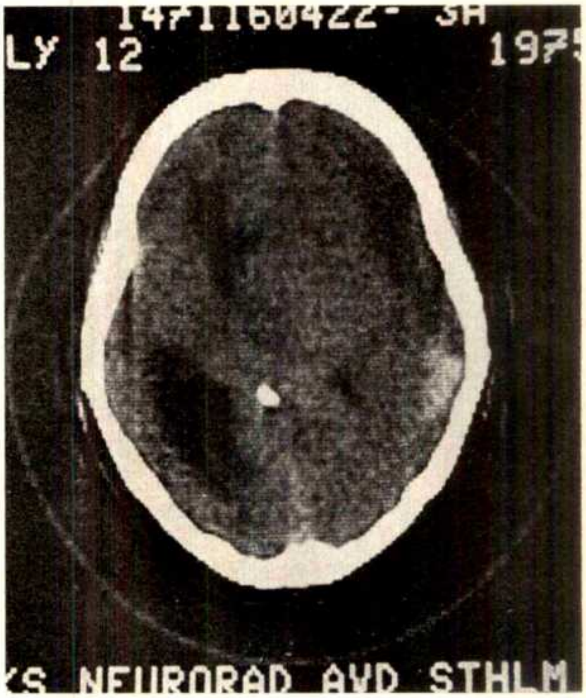
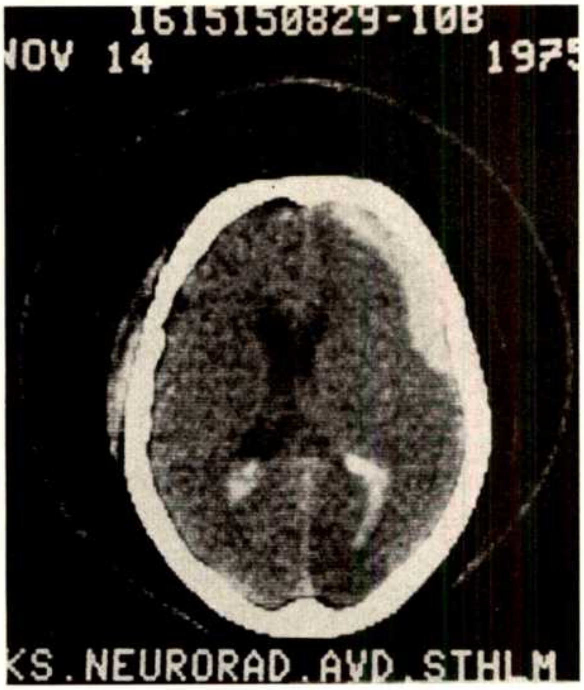


FIG. 6.

Patient No. 1471. Subdural haematoma on the right side with reduced attenuation anteriorly and increased posteriorly in supine position. About one week old. At operation liquefied contents found anteriorly and blood clots posteriorly.

blood clots were found in the lesions at operation. Blood clots were found in the declive parts of the lesions in both cases. The exact date of the head injury was uncertain in both patients but the injury probably occurred about one week before computer tomography in one case (1471) and two weeks in the other (1615).

Four lesions *could not be seen* at computer tomography (Table III). One of these, considered to be ten days old as estimated from the history, was



B

FIG. 5.

(A) A bilateral extracerebral interposition with reduced attenuation may be seen over the frontal lobes. Angiography three days later showed interposition without lateral displacement of the mid-line arteries. The lesion was not operated upon, but was considered to be a hygroma on the basis of clinical, angiographic and computer tomographic findings. The lateral ventricles are narrow frontally and dislocated posteriorly.

(B) Same patient two months later after a recent head injury. Subdural haematoma frontally on the right side, verified at operation. Fresh blood clots were found in the lesion. Blood is layered in both posterior horns. Slight displacement of the anterior horns to the left.

TABLE III

LESIONS NOT VISIBLE AT COMPUTER TOMOGRAPHY. PATIENT NO. 1268 MAY HAVE HAD AN EPIDURAL HAEMATOMA OWING TO FRACTURE OF THE SKULL IN THE SAME REGION AS THE LESIONS (RIGHT PARIETAL). PATIENTS NOS. 1268 AND 1368 MAY HAVE HAD AN INCREASED ATTENUATION, WHILE PATIENTS NOS. 1413 AND 1652 MAY HAVE HAD DECREASED ATTENUATION.

Pat. Code No.	Diagnosis	Verified	Depth	Comments
1268	Unknown	angio	4 mm	Fracture of the skull
1368	Epidural	op	4 mm	Fracture of the skull
1413	Subdural	op	10 mm	Three-week history
1652	Subdural	angio + op	8 mm	Liquefied contents

seen on the right side at angiography and was 4 mm thick. This patient also had a frontal liquefied subdural haematoma with low attenuation on the opposite side. Another patient (1368) had a frontal hygroma on the left side. Operation frontally on the right side revealed an epidural haematoma with a depth of 4 mm. In addition to several old-head injuries this patient had a fresh one two days before computer tomography and operation, resulting in a fracture of the skull on the right side at the site of the epidural haematoma (Fig. 4). The third lesion considered to be about three weeks old and not seen at computer tomography (1413), was found at operation to be a subdural haematoma with a depth of 10 mm temporally on the left side. Computer tomography, which was technically unsatisfactory due to artefacts produced by motion of the patient, had revealed a tumour in the left hemisphere, which was the reason for operation.

The fourth patient (1652) sustained a head injury three weeks before computer tomography. Angiography showed a parietal interposition on the left side not more than 8 mm thick. At operation a thin subdural haematoma with liquefied contents was found (Fig. 7).

Displacement of the ventricles was found in all patients, including the four in whom the lesions could not be seen.

Significant movement artefacts were present in two patients with reduced attenuation in the lesions (1268, 1629) and in one in whom the lesion was not visible (1413).

Of the four lesions not seen at computer tomography (Table III), two were estimated at operation to be 4 mm and 10 mm thick, respectively (1368, 1413) and one (1268) was found at angiography to be 4 mm thick. The fourth (1652) was recorded as 8 mm thick at angiography and was described as "thin" at operation. The two thickest lesions (1413, 1652) were operated upon and were subdural haematomas. One of them (1652) had liquefied contents and the other (1413) was not described in more detail but there was a history of head injury about three weeks before operation. The narrow lesion which was operated upon (1368) was an epidural haematoma. In the case of the lesion not operated upon (1268) there was a fresh fracture of the skull corresponding to the lesion.

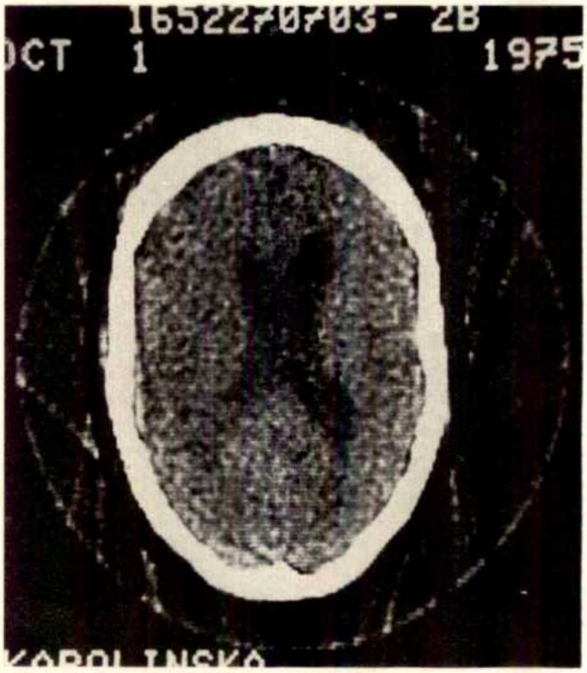


FIG. 7.

Surgically and angiographically verified subdural haematoma, about 8 mm thick, with liquefied contents parietally on left side. The lesion was not seen with certainty at computer tomography but the ventricles are displaced somewhat to the right.

Five other lesions detected at computer tomography were judged at the examination to be 10 mm or less in thickness (1588, 1588, 1630, 1654, 1268) (Table IV). Four of these had an increased attenuation while the fifth was reduced. In the latter case angiography showed a thickness of 13 mm. Of the narrow lesions with increased attenuation the thickness was reported at operation to be 10 mm in one patient (1588), while the thickness was not recorded at operation for two lesions (1588, 1630) and a narrow parietal haematoma was not operated upon or angiographied (Fig. 2).

TABLE IV

Narrow lesions visible at computer tomography. The only lesion with reduced attenuation (1268) appeared to be narrower at computer tomography than at angiography.

Pat. Code No.	Diagnosis	Attenuation	Depth DT	Verified	Depth
1588 right frontal	Subdural	increased	8 mm	op	not described
1588 left temporal	Epi + Subdur.	increased	7 mm	op	10 mm
1630 left frontal	Subdural	increased	10 mm	op	not described
1654 left parietal	Unknown	increased	5 mm	no	
1268 left frontal	Subdural	decreased	8 mm	angio + op	13 mm

TABLE V

The nine lesions examined by angiography, two of which were not seen at computer tomography. Bilateral angiography in patient no. 1525 showed a slow circulation bilaterally, but no avascular region.

Pat. Code No.	Diagnosis	Attenuation	Depth DT	Depth angio	Localization	Contents at op
1599	subdural	decreased	11 mm	12 mm	frontal	non op
1629	subdural	decreased	15	13	fr + par	liquefied
1612	subdural	mixed	12	13	fr + temp	liq + coag
1652	subdural	not visible		8	parietal	fluid
1525	epidural	increased	28	—	frontal	coagulated
1615	hygroma	decreased	16	13	frontal	non op
1684	epidural	increased	11	13	parietal	coagulated
1268	subdural	decreased	8	13	frontal	liquefied
1268	unknown	not visible		4	parietal	non op

One of the epidural haematomas proved to be 4 mm thick at operation (1368) and was not seen at computer tomography while the other three showed increased attenuation. The interval between head injury and computer tomography was short for all four epidural haematomas, and in the three visible epidural haematomas the shape was biconvex (Fig. 1). Fractures of the skull were found in connection with three of the epidural haematomas and in one of the two patients with mixed epi- and subdural haematomas.

Eight patients were subjected to angiography (Table V). One of these had two lesions and a total of nine lesions were thus examined by angiography. Seven of the lesions were detected by computer tomography. In one of the two lesions not seen (1268) a chronic subdural haematoma was observed on the opposite side both at computer tomography and at angiography. This haematoma caused displacement of the ventricles by 15 mm to the right, *i.e.* towards the side on which the narrow, 4 mm, non-visible lesion was found. This narrow lesion was not operated upon. The other lesion (1652) was found to be a chronic subdural haematoma at operation and angiography revealed a biconvex interposition 8 mm in depth. The patient had injured his head three weeks before the operation. Two more lesions were seen at computer tomography and angiography but were not operated upon. One of them (1615) was judged angiographically, by computer tomography and clinically to be a bilateral, frontal hygroma. The other (1599) had a typical, biconvex shape at angiography and a three-week history, consistent with the diagnosis of chronic subdural haematoma. The six remaining lesions were verified at operation. Angiography revealed all lesions and always showed dislocation of mid-line vessels.

Discussion

Ambrose (1974) and Scott *et al.* (1974) have shown that extravasated blood cells are responsible for the elevated absorption values in cerebral haematomas. Other authors have also considered that extravasation of red blood corpuscles causes increased attenuation (New *et al.*, 1974; Davis and Pressman, 1974; Baker *et al.*, 1975), whereas recent studies have indicated that the protein of haemoglobin also is responsible for the increased attenuation (Dreisbach *et al.*, 1976). Paxton and Ambrose (1974) showed that the density of "the peripheral bands", *i.e.* extracerebral haematomas, in patients with acute lesions correspond to those of clotted blood.

The lesions showing increased attenuation in the present study contained massive blood clots and had a short history of no more than a few days. One lesion with high attenuation (Fig. 3) was, according to the operation report, both liquid and contained blood clots. The attenuation was, however, distinctly increased in the entire lesion and the history was short, suggesting that the clots of blood dominated.

The group of lesions with increased attenuation contained all the epidural haematomas except the 4 mm thin epidural haematoma which was not seen (1368).

The epidural haematomas were biconvex in shape and were usually combined with fracture of the skull (Fig. 1). The subdural haematomas had one of three shapes illustrated in Fig. 8.

The lesions with reduced attenuation were either hygromas (Fig. 4) or chronic subdural haematomas, and the contents were liquid blood or clear fluid. Previous studies have shown that old liquefied haematomas have a reduced attenuation (Levander *et al.*, 1975; Cronquist *et al.*, 1975; Ambrose, 1974; Scott *et al.*, 1974; Davis and Pressman, 1974). The patients in the present study had either sustained head injuries long before computer tomography or the history of head injury was uncertain. This group contained alcoholics with several previous head injuries or epileptic attacks, and patients with gradually increasing impairment of consciousness or disorientation, in some cases without a definite history of head injury.

The two lesions with mixed attenuation occupied an intermediate position as regards the time interval between injury and computer tomography. These patients belong to the group subacute or subchronic subdural haematoma. In both cases the parts of the lesions which were found to have increased attenuation were dependent, probably due to sedimentation (Fig. 6).

Thus, there appears to be a clear correlation between increased attenuation, blood clots or blood in the lesions and a short interval between head injury and examination by computer tomography. The epidural haematomas belong to this group.

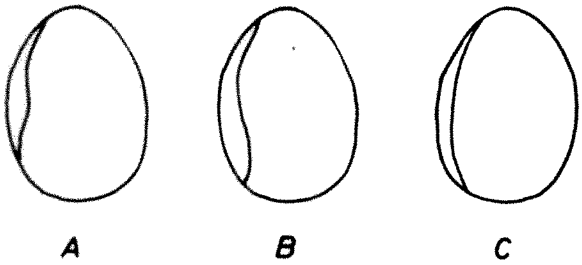


FIG. 8.

The three principal shapes of the subdural haematomas. All chronic subdural haematomas had the shape indicated in C.

In model experiments (McCullough and Payne, 1976) the resolving power for low contrast objects with the EMI-head scanner varied between 2 and 9 mm. The results in this clinical study seem to corroborate this since thin haematomas were occasionally missed. The two thickest lesions not seen at computer tomography may be designated as old subdural haematomas. One of them (1652) contained fluid at operation and the other (1413) had a three-week history and was a subdural haematoma. These should have shown reduced attenuation. The two thinner lesions (1268, 1368) should have shown increased attenuation. One of them (1368) was an epidural haematoma. The other (1268) had a fracture of the skull corresponding to the lesion and was probably an epidural haematoma. This may indicate that narrow lesions with increased attenuation are easier to detect than lesions with reduced attenuation. This assumption is supported by the finding that of the five narrow lesions below 10 mm seen at computer tomography, four had increased attenuation (Tables III and IV). The fifth (1268 left frontal) showed reduced attenuation and was 13 mm thick at angiography.

The finding that old, thin lesions may be overlooked may to some extent be due to overswing, which may mask lesions with reduced attenuation. Movement artefacts may also render diagnosis more difficult. A more plausible explanation is partial volume effects which become significant especially high up on the convexity where the surface of bone forms a wide angle with the long axis of the pixcells. Narrow haematomas below the vertex may thus be overlooked because they are masked by the combination of bone to the attenuation value of adjacent tissue. This can to some extent be avoided by tilting the skull in the scanner so that the beam is at 90 deg. to the bone of the calvarium and the underlying lesion, as has previously been shown (Levander *et al.*, 1975) (Figs. 9 and 10).

An important indirect aid in the diagnosis of traumatic extracerebral lesions is the position of the ventricles as pointed out by several authors (Levander *et al.*, 1975; Ambrose, 1974; Scott *et al.*, 1974; Davis and Pressman, 1974; Paxton and Ambrose, 1974; Kistler *et al.*, 1975; Kramer *et al.*, 1975). Although Ambrose (1973) could identify only one of the seven subdural haematomas using the 80×80 matrix, the ventricles were displaced in all seven patients. The ventricles were displaced in all patients in the present study, either to one side or in an antero-posterior direction. In one patient a narrow haematoma was somewhat masked by a large extracerebral haematoma on the opposite side which

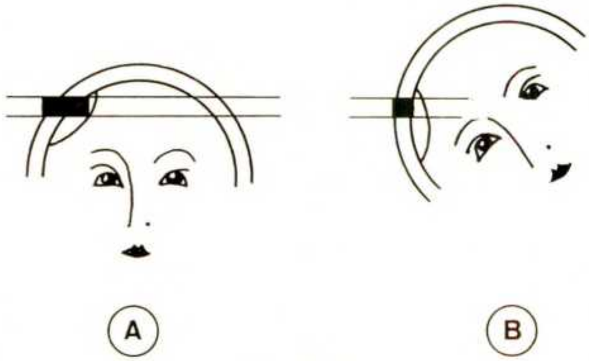
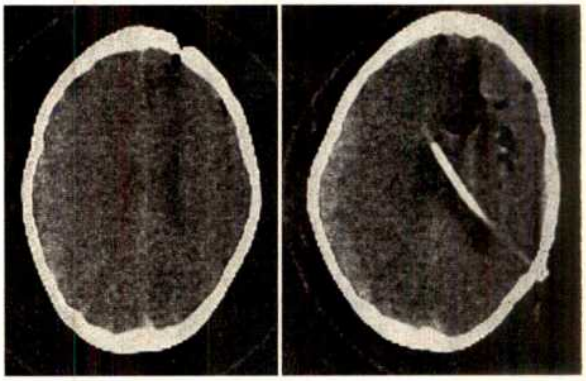


FIG. 9.

Sketch showing extracerebral haematoma near the vertex. (A) Horizontal standard section. A large part of the haematoma will be masked by the high attenuation of the bone. (B) With the head tilted in relation to the tomographic plane there is less risk of partial volume effects masking the haematoma because the beam is at 90 deg. to the bone and to the lesion.



A B

FIG. 10.

Patient No. 1756, not included in the study. Subdural haematoma.

(A) Horizontal standard section shows a possible increase of attenuation on the left side. On diagonal section (B) the haematoma is seen at the same level more distinctly and is better defined against the surface of the brain.

displaced the ventricles towards the narrow haematoma (1268). Davis and Pressman (1974) have pointed out the risk of small lesions with the same degree of attenuation as the brain being overlooked if the ventricles are not displaced. A good idea of the position of the ventricles could be obtained in this material even in patients in whom there were significant movement artefacts. If the ventricles are displaced and no other lesions of the brain are seen, an extracerebral lesion should be suspected.

Angiography revealed all nine lesions and dislocation of mid-line vessels in eight patients, while computer tomography revealed only seven of the lesions (Table V). Hence, angiography seems to be a more reliable diagnostic aid for detecting small extracerebral lesions. Angiography gives no information on the contents of the lesions and is less reliable than computer tomography for detection of concurrent traumatic intracerebral lesions (Levander *et al.*, 1975).

CONCLUSIONS

1. Recent extracerebral traumatic lesions (no more than five days old) including epidural haematomas have a higher attenuation than that of the brain.
2. Old lesions, such as hygromas or chronic subdural haematomas, have a lower attenuation than that of the brain. These lesions were at least ten days old.
3. Lesions with mixed attenuation represent an intermediate group of subacute, subchronic subdural haematomas in which the contents are liquefied but mixed with blood clots which are usually situated in dependent parts of the lesions.
4. Displacement of the ventricles without other lesions of the brain may indicate extracerebral, intracranial lesions.
5. Narrow lesions with reduced attenuation appear to be more difficult to detect by computer tomography than narrow lesions with increased attenuation.
6. As expected from angiographic experience epidural haematomas were usually biconvex in shape while subdural haematomas were at least partially concave towards the surface of the brain (Fig. 8).
7. Angiography is a more reliable diagnostic aid than computer tomography when only extracerebral lesions are present. Computer tomography generally provides better information on the nature, localization and extent of other, concurrent cerebral lesions.

ACKNOWLEDGMENT

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Book review

Röntgenunterschung in der Orthopädie. Methode und Technik. By E. Hafner and H. Ch. Meuli, pp. 199, 1975 (Bern, Verlag Hans Huber), DM141.

This book, which is written in German, provides a simplified guide to standard radiographic examinations used in the diagnosis of musculo-skeletal disease. The authors' intentions are to promote the acceptance of certain standardized radiographic projections which can be easily reproduced in wide general use, either in hospital or clinic.

This simplistic approach will be of particular interest to radiographers, radiologists and orthopaedic surgeons in the earlier part of their training. The work is not sufficiently comprehensive to be of any great value to those with more experience. For example, there is no indication of the value of special radiographic projections in difficult areas of the spine, *e.g.* odontoid peg region or cervico-dorsal junction. Perhaps it is intended to dwell more comprehensively on this in subsequent editions.

Much use is made of line-drawings which illustrate the radiographic positioning very clearly indeed. Unfortunately, there is a loss of quality in the reproduction of a few of the radiographs.

J. L. Harris.

1976, *British Journal of Radiology*, *49*, 1013–1017 DECEMBER 1976

Myoepithelial activity and the appearances of sialograms: a possible role in the formation of sialectasis

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ABSTRACT

In experimental studies on dogs it has been shown that the sialographic filling of the ductal system may be severely restricted if the myoepithelial cells are contracting and it seems likely that myoepithelial activity in man will also influence sialographic appearances. It has also been found that when secretory forces were accompanied by myoepithelial contraction against a sialographic pressure the ensuing damage to striated ducts produced appearances of sialectasis. It is wondered whether similar events may sometimes be responsible for sialectatic appearances in man.

Recent work on the backward movement of fluids from the duct of submandibular glands in anaesthetized dogs, using solutions of the marker substance horseradish peroxidase, have shown that there is a ready back-diffusion into the interstices of the gland, whether the movement be induced by a small injection or by a head of pressure (Parsons and Garrett, 1976). However, it was predicted that the events may be different if the myoepithelial cells, which embrace the acini and intercalary ducts, were contracting.

As a result of studying pressure changes induced in the duct system, which were attributed to myoepithelial contractions (Emmelin *et al.*, 1968), it was considered that myoepithelial contraction may afford support to the underlying parenchyma against back pressures. In the dog one is able to differentiate submandibular sympathetic secretion which is a β-adrenoceptor function (Emmelin and Holmberg, 1967) from myoepithelial contraction which is an α-adrenoceptor function (Emmelin *et al.*, 1969). Using appropriate blocking or stimulating drugs, it has been possible to test the supportive role of myoepithelial contraction against a head of pressure (Emmelin *et al.*, 1976a, b). Thus it was found that when the outflow from a system connected to a cannula in the submandibular duct was raised 25–50 cm above gland level, secretion from sympathetic stimulation continued unabated, but when myoepithelial activity was blocked by dihydroergotamine the sympathetic secretion ceased if the outflow were raised although it still occurred when the outflow was returned to gland level. Furthermore when myoepithelial contraction was induced without secretion by the α-activating drug phenylephrine or by bradykinin the gland was better able to support a column of fluid than in its passive state. Histological examination of the tissues showed that in the latter experiments myoepithelial contractions helped to contain much of the preformed saliva in the ducts but it was lost from the ducts into the interstitial spaces of the glands when the outflow was raised in passive glands. This suggested the probability that myoepithelial activity could influence sialographic appearances. In the secretory experiments the glands continued to secrete against a head of pressure so long as the myoepithelial cells were contracting. However, this caused ballooning distension of many of the striated ducts and these ducts are the first parts around the luminal system not supported by myoepithelial cells. It therefore seemed possible that, if such changes were to occur to striated ducts during sialography, this might lead to appearances of sialectasis.

The purpose of the present investigation was to examine the effects of myoepithelial contractions on sialographic filling of glands and to explore the possibility that secretion aided by myoepithelial contraction against a sialographic pressure may cause appearances of sialectasis.

MATERIALS AND METHODS

Six dogs weighing 10–30 kg were used after anaesthetizing with Nembutal (Abbott) 30 mg/kg I.V. Additional doses of Nembutal were given as required.

Both submandibular ducts were exposed in the neck and cannulated with the widest bore polythene tubing that was possible. The trunks of the autonomic nerves supplying the glands were cut prior to sialography in order to prevent any reflex events in the glands and to allow controlled stimulation of them. Both lingual nerves were sectioned, and in each case the peripheral stump was electrically stimulated (6–10 Hz at 8–10 V), using bipolar electrodes, to induce parasympathetic secretion by the glands. Similarly the vago-sympathetic trunk was sectioned and the peripheral end was stimulated (2–20 Hz at 20 V) in order to induce sympathetic effects in the gland.

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Hypaque (Winthrop), Triosil 440 (Nyegaard, Oslo) and Lipiodol (May & Baker), were each used for sialography and the fluid was introduced either by injection from a Mantoux syringe connected to the cannula or by gravity feed from a Mantoux syringe, without plunger, connected by wide bore flexible tubing to the cannula and held vertically with the zero line of the syringe at 50–70 cm above the gland.

In some experiments the effects on sialographic appearances of sympathetic myoepithelial contraction *per se* were tested by stimulating the sympathetic nerve after blocking secretion by the β-blocking drug propranolol (1–1.5 mg/kg I.V.). In the remaining experiments the effects of sympathetic stimulation causing both myoepithelial contraction and secretion were tested.

Radiographs were taken by a Philips Oralix at 50 kv on quarter-plate dental films (Kodak occlusal ultra-speed D safety-1-film) placed under the glands on the operating table.

The glands were subsequently examined by routine histological procedures.

RESULTS

The approach to this study was of necessity somewhat empirical and, as one began to understand the problems, one became more adept at handling them by adopting different ploys. It was often possible to do a number of sialographic tests on each gland and for this it was found beneficial to open the system and induce parasympathetic secretion for 30–60 seconds between manoeuvres in order to wash out the gland.

Initially the gravity feed was rather slow and the ductal filling not always good. It was thought that this may have been due to the extreme viscosity that develops in submandibular saliva in dogs when it remains in the glands for any length of time. Therefore in later experiments prior stimulation of the parasympathetic nerve at 6–8 Hz for 20–30 minutes, in order to induce a copious secretion, was regularly carried out, since a similar procedure was previously shown to improve the pressure responses attributed to myoepithelial activity by Emmelin *et al.* (1969). After this procedure good filling of the luminal system by 0.2–0.6 ml (depending on the size of the animal) was readily achieved within about 30 seconds by gravity feed.

It was soon found the Triosil gave satisfactory results and in subsequent experiments this material alone was used.

EFFECTS OF MYOEPITHELIAL CONTRACTIONS ALONE

This was studied after blocking sympathetic secretory effects with propranolol.

In the first experiments a gravity feed sialogram was initially taken immediately after clamping the

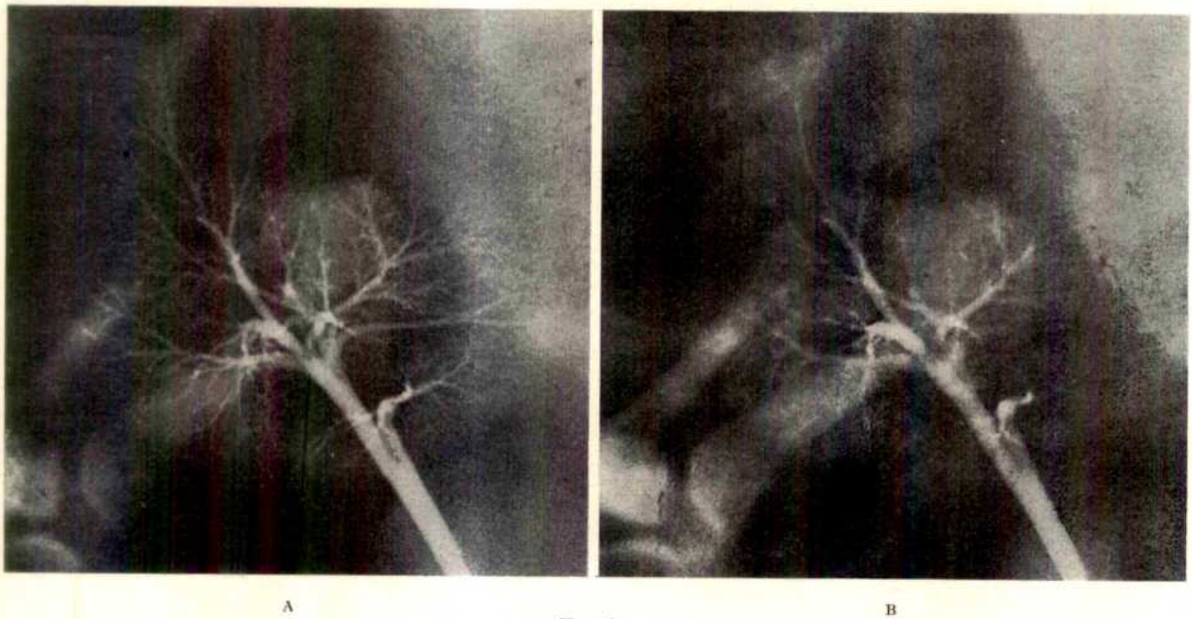
A B

FIG. 1.

(A) Submandibular sialogram of a dog, after passive filling from 50 cm (0.45 ml in 20 seconds).
(B) Second sialogram taken at the end of the tenth second of sympathetic stimulation of 3 Hz, started immediately after (A), (β-adrenergic secretory effects had been blocked by propranolol 1.5 mg/kg). Note the extensive reduction in luminal filling.

tubing when sufficient fluid had passed into the ducts, then the system was unclamped and sympathetic stimulation was started at 3–5 Hz, in order to contract the myoepithelial cells, and a second picture was taken at the end of the tenth second of stimulation. In one experiment, after passive filling of 0.45 ml, sympathetic stimulation at 3 Hz expelled about 0.065 ml against an outflow height of 50 cm and held it there during the stimulation period of ten seconds and, as seen in Fig. 1, there was a remarkable expulsion of sialographic fluid from the duct system. In this animal stimulation at 2 Hz caused an initial small return of fluid into the syringe but then it proceeded to move backwards into the gland, indicating that insufficient myoepithelial tone had been induced at this rate to uphold the column of fluid.

In other experiments the effects of stimulating the sympathetic nerve at 3–5 Hz from the onset were tested on gravity feed sialography from 50 cm over set times (30–60 seconds), then stimulation was discontinued and a second sialogram was taken after the same time. This led to a big increase in the amount of sialographic material in the finer ducts in the second X ray.

Comparisons were also made between the sialographic appearances of passive glands resulting from gravity filling for 30 seconds from a height of 50 cm, and the amount of filling of the same glands at 30 seconds, 60 seconds and longer during sympathetic stimulation at 3–5 Hz. In these experiments parasympathetic stimulation was performed after each sialogram in order to wash out the gland. Less fluid passed into the gland during sympathetic stimulation than in the passive state and there was correspondingly little or no filling of the finer luminal channels radiographically. Thus in one animal whereas 0.2 ml passed into the passive gland in 30 seconds, only 0.07 ml moved towards the gland in the same time during sympathetic stimulation at 4 Hz and no radio-opaque fluid was detectable in the gland. After one minute the volume was only 0.11 ml and although this displayed the larger intraglandular ducts none of the smaller ones were visible. During longer times in this type of experiment the movement of fluid into the gland gradually increased but only at a slow rate. In one instance an isolated patch of punctate sialectasis occurred with prolonged stimulation of the myoepithelial cells against a sialographic head of pressure.

EFFECTS OF MYOEPITHELIAL CONTRACTIONS PLUS SECRETIONS

In all experiments, whether made by gravity feed or by injection, sympathetic stimulation at 20 Hz was always capable of creating a form of sialectasis (see Fig. 2). This was more apparent when the luminal system had been filled with sialographic

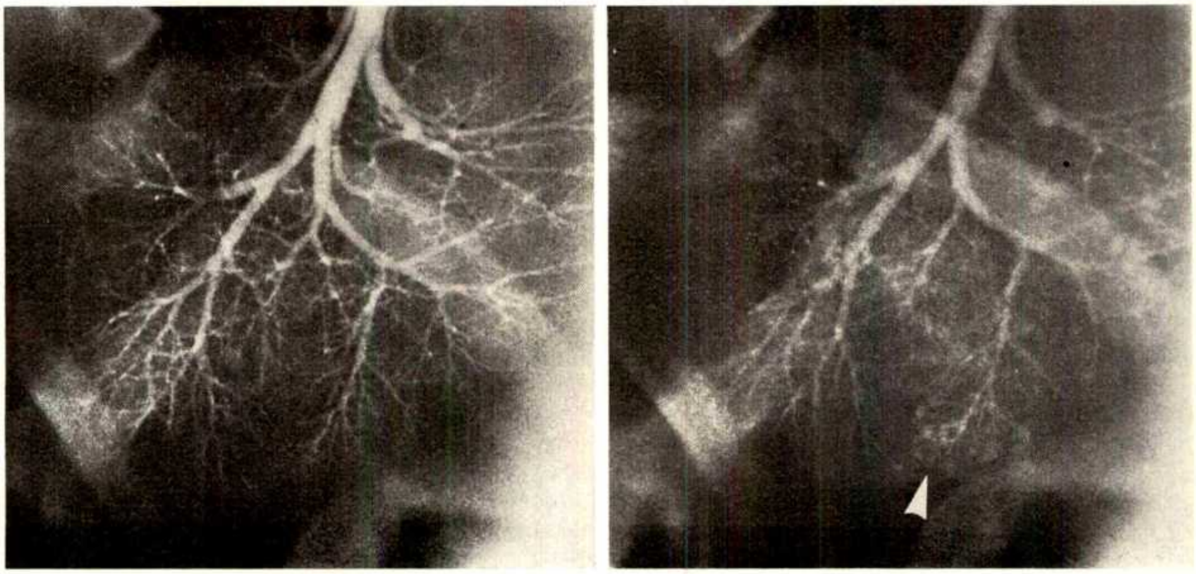
A B

FIG. 2.

(A) Submandibular sialogram of another dog, after passive filling from 70 cm (0.5 ml in 40 seconds).
(B) Second sialogram after 20 seconds of sympathetic stimulation at 20 Hz, started immediately after (A) to induce myoepithelial contraction plus secretion. Note the reduction in luminal filling and the emergence of sialectatic appearances, especially at ↑.

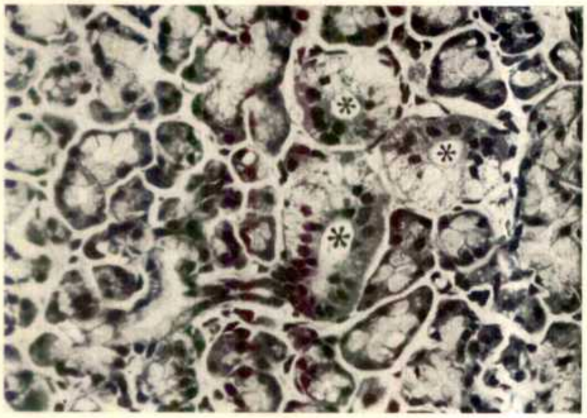

FIG. 3.

Section of the submandibular gland in Fig. 2 through the marked area of sialectasis showing ballooning of three striated ducts (*), the largest of which is connected to an intercalary duct leading to an acinar complex (H. & E. × 275).

fluid first, *i.e.* before nerve stimulation, but it was also seen faintly when the stimulation and the opening of the gravity feed system were carried out simultaneously. If prolonged stimulation or too forceful injection were used extravasation of sialographic fluid into the gland occurred.

HISTOLOGY

Oedematous damage of striated ducts, similar to that described by Emmelin *et al.* (1976b), was readily evident in those glands in which sialectasis had been induced (see Fig. 3).

DISCUSSION

In the non-secreting experiments it was dramatically shown that the ability for displaying the ductal system sialographically was greatly reduced when the myoepithelial cells were contracting at sub-maximal stimulation rates. Myoepithelial activity, therefore, may play a similar role in limiting the ductal display in some human patients, whose glands otherwise appear to be essentially normal. It is likely that in conscious patients the events of sialography will cause variable reflexogenic stimulation of the secretomotor nerves of the gland, which in turn will affect the quantity of fluid allowed to pass into the ducts. It is not known whether separate motor nerves exist from the secretory ones. Ultrastructural studies of the glandular nerves in man (Garrett, 1967) and other species (Garrett, 1972) indicate that it is likely that the same axons supply both secretory and myoepithelial cells along their course. Nevertheless, it is possible that myoepithelial contractions can occur in the absence or minimum of secretion, for in appropriate experimental studies the myoepithelial cells have been found more sensitive to drugs and nerve impulses than the secretory function (Emmelin *et al.*, 1969). Although sympathetic effects were studied in the present work for reasons of convenience, it should be realized that cholinergic nerves also induce myoepithelial contractions in all species so far tested (Emmelin *et al.*, 1968; Thulin, 1975, 1976; Emmelin and Gjörstrup, 1976).

The changes seen in Fig. 1 may seem hard to reconcile with the fact that the fluid has only been displaced mechanically. It is, however, unlikely that we had previously achieved total filling of all the luminal spaces, acinar as well as ductal, with sialographic fluid since precautions were taken to avoid over-filling the gland. Thus expulsion of precontained saliva from the acinar lumina on myoepithelial contraction will have displaced and to some extent diluted sialographic fluid previously held in the ductal spaces.

It has now been shown that, when sympathetic secretion against a head of pressure is also accompanied by myoepithelial contraction, it not only causes ballooning disruption of striated ducts as demonstrated by Emmelin *et al.* (1976b) but this may also lead to sialographic appearances of sialectasis. It is unlikely, with the poor resolution afforded, that this can ever be attributable to individual striated ducts but it is probably seen when a number of similarly affected ducts are superimposed in a relatively small area.

It was of interest that on repeating simple sialography this sometimes failed to reproduce the sialectatic appearances seen previously, which makes it likely that after the damage has occurred there is diffusion away of the contained fluid and the luminal side becomes self sealing unless disrupted by further undue pressure. However, with greater pressures sialectasis could be reintroduced and then it sometimes appeared as if sialographic fluid were passing preferentially to such sites. The histological fate of these damaged ducts is not known but it is not unreasonable to believe that, given time, they return to normal.

It is wondered whether similar events in man may be responsible for some sialectatic appearances. Very little is understood about structural changes accompanying human sialectasis. It is unlikely that the foregoing type of event is responsible for the appearances in Sjögren's and sicca syndrome. However, in more normal glands with a greater secretory capacity it seems a distinct possibility and may afford a possible explanation for some types of juvenile sialectasis. As mentioned previously reflex stimulation of the gland seems inevitable during sialography and if this were to produce myoepithelial contractions plus secretion against a sialographic pressure then similar damage to the ducts may occur. In such patients at other times minor obstructions may evoke similar events which would tend to aggravate the recurrent episodes of parotitis to which these patients are subject. It would be informative, if ever the possibility arose, to see whether the sialectatic appearances disappeared on repeating sialography under general anaesthesia.

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The röntgenographic findings in the acute neuronopathic form of Niemann-Pick disease

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Abstract

The röntgenographic changes are described in two patients with the acute neuronopathic form of Niemann-Pick disease. These consist of metaphyseal splaying, osteoporosis and the quadrate appearance of the lumbar vertebrae with relatively long pedicles. The parenchymatous involvement is manifested by interstitial lung changes, enlargement of liver, spleen and kidney and distended intestinal loops with an abnormal mucosal pattern associated with prolonged transit time of the contrast material. The differential diagnosis of the above changes is discussed.

Niemann-Pick disease (N.P.D.) is a sphingomyelin lipidosis characterized by a sphingomyelinase deficiency associated with the production and accumulation of "foam cells" in the reticuloendothelial system (Fredrickson and Sloan, 1972b). This inborn error of phospholipid metabolism has been classified into five types: Type A—the acute neuronopathic form; Type B—the chronic form without central nervous system involvement; Type C—the subacute form with central nervous system involvement; Type D—the Nova-Scotia variant; Type E—the indeterminate form in adults (Crocker and Farber, 1958; Crocker, 1961; Fredrickson and Sloan, 1972b).

The acute neuronopathic form of N.P.D. is rapidly fatal in infancy, the patient usually failing to survive beyond the second year of life. The disease involves the nervous system, the bony skeleton, the lungs, the liver and spleen, the gastrointestinal tract, the lymph nodes and the kidneys.

Röntgenological descriptions of N.P.D., particularly in relation to the separate forms, are very scant with the exception of the report by Lachman *et al.* (1974). It is the purpose of this presentation to demonstrate the röntgenographic changes found in the acute neuronopathic form of this disease as the other types show few of these changes.

Case Report

Case A

The parents of this seven-month-old male infant, who was an only child, were first-cousins of Jewish Oriental origin. The mother's sister was known to have hepato-splenomegaly and lymphadenopathy. Pregnancy had been uneventful and the infant's birth weight was 3680 g.

The infant was hospitalized because of failure to thrive, abdominal distention, cough and fever. Physical examination revealed a cachectic infant weighing 6100 g and with a pale-brownish skin colour. Fundus examination showed no pathological findings. Decreased breath sounds and râles were heard over the right chest. The abdomen was markedly distended and the liver and spleen were enlarged, reaching the iliac crest. Generalized muscle weakness was noted. Psychological tests showed that the patient was functioning at the level of a three-month-old infant.

Laboratory findings: haemoglobin 7.7 g%, erythrocytes 2.7 million, leucocytes 6000 with a normal differential count, thrombocytes 80000, total protein 5.5 g%; electrophoresis on paper—albumin 60%, alpha 1–6%, alpha 2–9%, beta 9% and gamma 15%; cholesterol 123 mg%, alkaline phosphatase 6 Armstrong King units. Examination of the bone marrow revealed cells with a vacuolar cytoplasm. The patient was suspected to have infantile type of Gaucher's disease. His condition deteriorated and he died at 15 months. Histological and histochemical examination disclosed that the pons, medulla oblongata, cerebellum, liver, spleen, lymph nodes, bone marrow, lung parenchyma, kidney, adrenals, the ganglia of Meisner and the plexus of Auerbach were all infiltrated with cells storing a phospholipid substance. Phase microscope showed that these cells had the features characteristic of N.P.D.

Chest röntgenograms demonstrated a reticular pattern in the right suprahilar region and in both lower lung fields. In several areas this merged into a non-homogeneous shadow (Fig. 1). These findings were persistent throughout the whole period of hospitalization.

The hand röntgenogram showed a bone age of three months (chronological age seven months) with osteoporosis and metaphyseal splaying of the distal radius (Fig. 2A). The röntgenogram of the knee region demonstrated splaying of the bones with a thin cortex along the diaphysis, and porosis also affecting the epiphyses (Fig. 2B). The bulk of the muscles was reduced along the bones, with an increase in the intermuscular fat septa.

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Case B

This six-month-old girl of Arabic origin had two healthy siblings and her parents were not consanguineous. Pregnancy and delivery had been normal; birthweight was 3500 g. Development had been normal until the age of three months, when there was a decrease in appetite and her abdomen appeared swollen. She was hospitalized because of vomiting and diarrhoea. Physical examination revealed a cachetic, dyspnoeic infant. The head was triangular in shape with hypotelorism and a large, protruding tongue. Fundus examination revealed the cherry-red spot. Râles were heard over the right chest. The abdomen was markedly distended with no abnormal peristaltic sounds. The liver and spleen were hard and enlarged, reaching the iliac crest. Head circumference, weight and length were all below the 3rd percentile.

Laboratory tests showed a haemoglobin level of 7.6–10.7 g%. The rest of the haematological work-up was normal. Serum electrolytes and proteins were normal. Alkaline phosphatase was 12 Bessey-Lowry units, cholesterol 150–173 mg%, total lipids 473–483 mg%, triglycerides 146 mg%, transaminase 252–300 units. Electrophoresis of lipoproteins was normal.

Examination of the bone marrow disclosed reticulum cells with a vacuolar cytoplasma and an eccentric nucleus, changes which were suspected to indicate a storage disease. An open liver biopsy was performed and the chromatographic examination of the specimens revealed a pathologic accumulation of sphingomyelin. Examination of the liver tissue by light and electron microscope disclosed cells with the characteristic features found in N.P.D. Because of the persistent distension of the intestinal loops a biopsy was performed at the level of the duodeno-jejunal flexure. Examination of the specimen demonstrate flat villi and N.P. cells within the lamina propria of the mucosa.

Repeated chest röntgenograms showed bilateral hyperinflation and a persistent reticular pattern throughout both lung fields with consolidation in the right suprahilar region and left lower lobe. The heart was normal (Fig. 3).

The long bones, including the epiphyses, demonstrated osteoporosis. All the metaphyses were

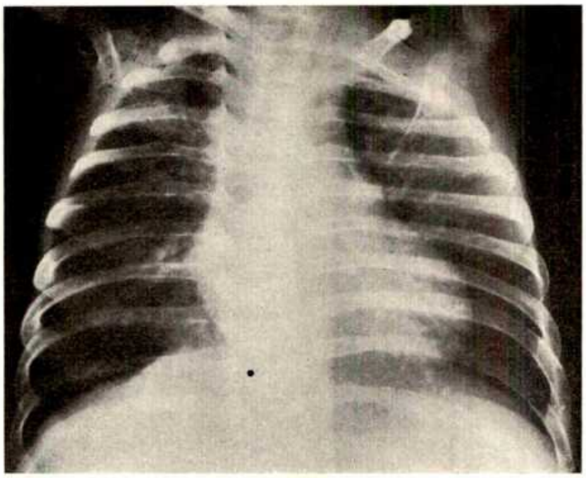
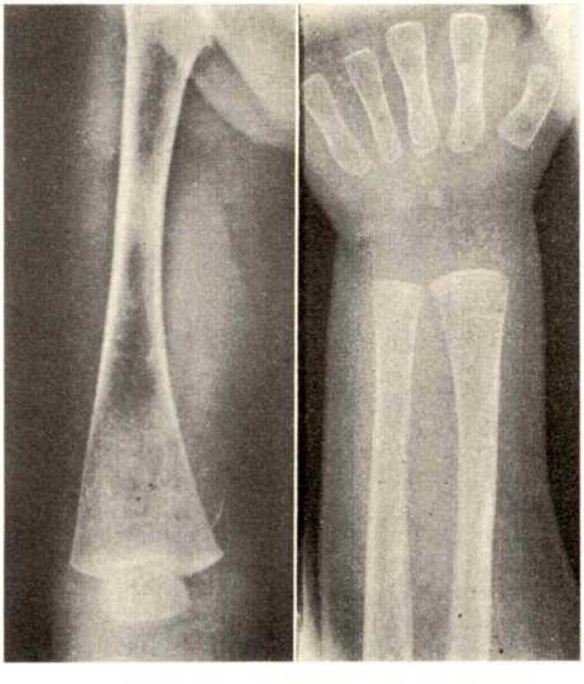


FIG. 1. *Case A.*
Chest röntgenogram. The heart appears normal. A non-homogeneous shadow in the right upper lung field and in both lower lobes.



A B

FIG. 2. *Case A.*
Röntgenograms of the long bones (A) the distal femur; (B) the distal forearm. Porosis of the diaphyses and the epiphyses with pencil-like thin cortices and splaying of the metaphyses, especially of the distal femur (A). Bone age three months, normal modelling appearance of the metacarpal bones (B).

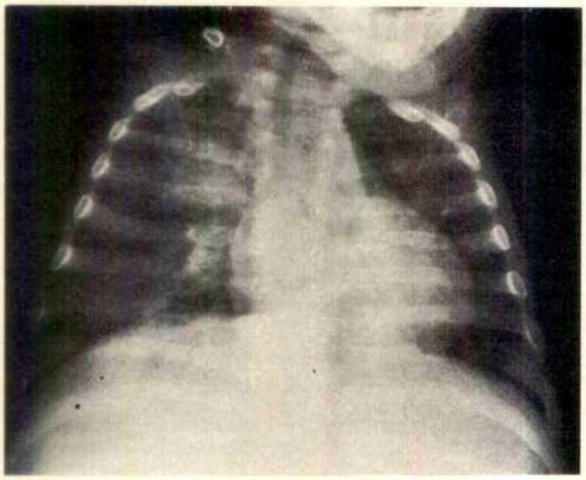


Fig. 3. *Case B.*

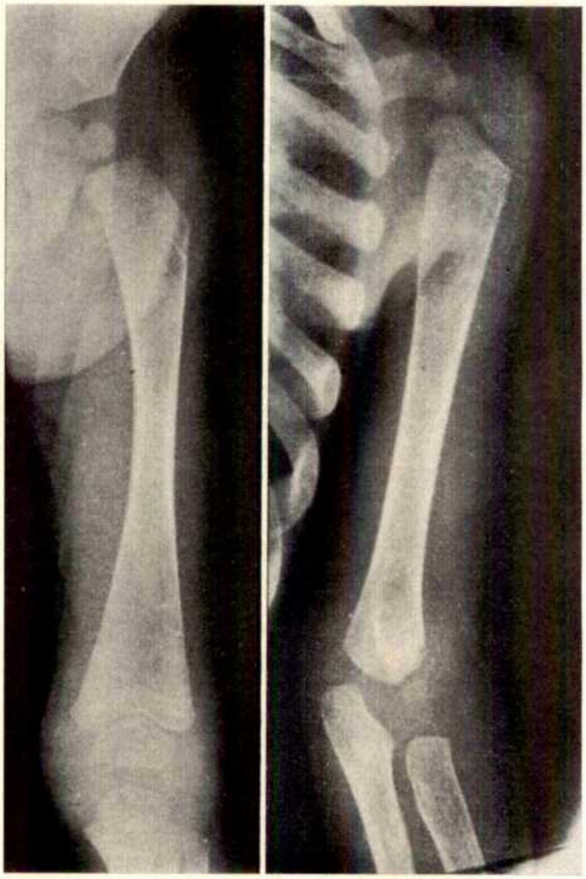
Chest röntgenogram. Non-homogeneous infiltrates in the anterior segment of the right upper lobe and the left lower lobe. Bilateral hyperinflation.

splayed, most markedly in the distal femur (Fig. 4A); bilateral coxa valga was present. A notch was seen on the medial aspect of the proximal metaphyseal region of the humerus (Fig. 4B). Bone age corresponded to six months at the chronological age of 12 months. The bulk of the muscles was reduced with increased intermuscular fat septa. The lumbar vertebral bodies were porotic and were rectangular in appearance with relatively long pedicles (Fig. 5). No beaking or notching was visible.

Plain films of the abdomen, repeatedly, disclosed permanently distended intestinal loops without air-fluid levels. The marked hepato-splenomegaly displaced the distended bowels medially. No ascites was present. Gastrointestinal examination showed dilated small intestine lacking mucosal folds. No narrow segments were visible. The caecum, ascending colon and transverse colon were broader than normal with thick mucosal folds. The transit time of the contrast material was markedly increased (Fig. 6).

Intravenous pyelography demonstrated a normal excretory system but both kidneys were generally enlarged. The kidney borders were smooth (Fig. 7). No abnormal calcifications were seen.

Two days after the infant's admission the vomiting and diarrhoea stopped although the abdomen continued to be distended. During the ten months in which this child has been hospitalized her condition has deteriorated. The hepato-splenomegaly has increased and the dyspnoea has become worse.



A B

Fig. 4. *Case B.*

Röntgenograms of the long bones: (A) femur, (B) humerus. Marked porosis including the epiphyseal centres with thin cortex along the diaphyses and medullary cavity expansion. Splaying of the metaphyses (A). Medial notching defect in the metaphyseal region of the proximal humerus (B). Reduction of the muscle bulk around the bones.

Discussion

Both of these cases fulfil the criteria for the diagnosis of the acute neuronopathic form of N.P.D. The absence of the cherry-red spot in Case A does not interfere with this diagnosis (Fredrickson and Sloan, 1972b).

The basic pathological change in N.P.D. is the accumulation of sphingomyelin in the reticulo-endothelial cells of the various body systems and organs. The accumulation of a large number of N.P. cells within the bone marrow results in trabecular bone resorption and the appearance of osteoporosis, thinning of the cortical bone and widening of the medullary cavity. In the more advanced stages of the disease splaying of the metaphyses develops (Figs. 2,

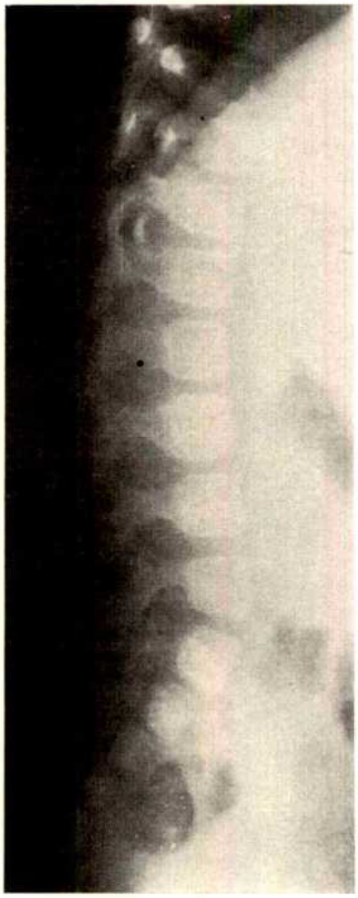


FIG. 5. *Case B.*
Lumbar spine—lateral view. Lumbar kyphosis. Quadrate appearance of the vertebral bodies with porosis. Relatively long pedicles.

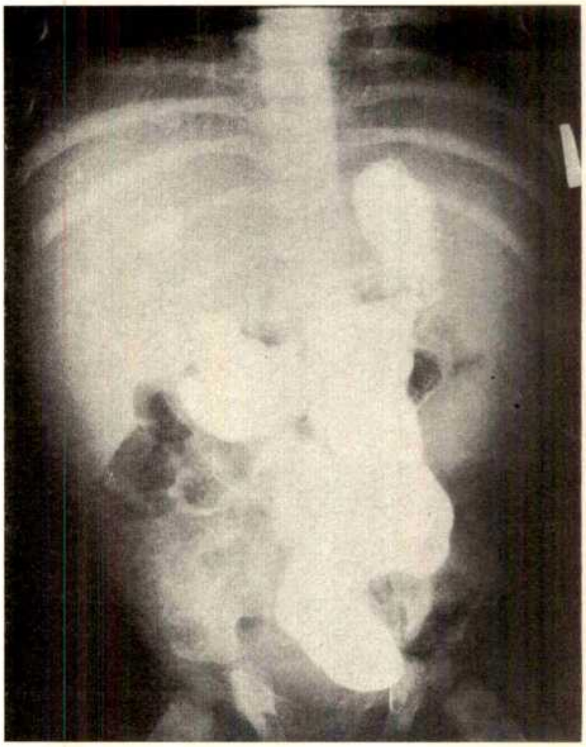


FIG. 6. *Case B.*
Small bowel examination. After three hours, some contrast material is still evident in the stomach. The duodenum and jejunal loops, which are still filled with contrast material, are wide, with no mucosal folds. Hepatosplenomegaly.

4) (Gildenhorn and Amromin, 1961; Moseley, 1964; Lachman *et al.*, 1974). In Case B the vertebrae were osteoporotic with a quadrate appearance and relatively long pedicles (Fig. 5). These spinal changes, and the coxa valga (Swischuck, 1970) are not characteristic findings in N.P.D. but must be considered within the general framework of changes present in cases in which there is a nervous system disturbance and/or impairment of muscular function. Also to be considered within the same context is the appearance of the decrease in the muscle bulk accompanied by enlarged fat septa.

In the lungs, the pathological accumulation of the substrate in the reticuloendothelial cells is responsible for the "unresolved pneumonic appearance" and the reticular pattern (Figs. 1, 3) (Crocker and Farber, 1958; Gildenhorn and Amromin, 1961; Moseley, 1964; Fredrickson and Sloan, 1972; Lachman *et al.*, 1974).

Although hepato-splenomegaly is not a röntgenographic diagnosis, in the cases of the acute neuronopathic form of the disease it is quite massive and displaces the intestinal loops medially. The bowel loops are permanently distended with a lack of mucosal folds. This is accompanied by a relatively long transit time of the contrast material. These manifestations can be explained by the hypotonicity and the disturbance in the function of the intestinal absorbtion caused by N.P. cell infiltration of the walls, villi, and the various nervous plexuses as found in the autopsy of Case A and the intestinal biopsy of Case B (Fig. 6) (Fredrickson and Sloan, 1972b). It is probable that the cachectic appearance of the patient can be explained on the basis of these gastrointestinal changes.

According to Fredrickson and Sloan (1972b), there are often foam cells present in the glomeruli and the tubules of the kidneys. These pathologic

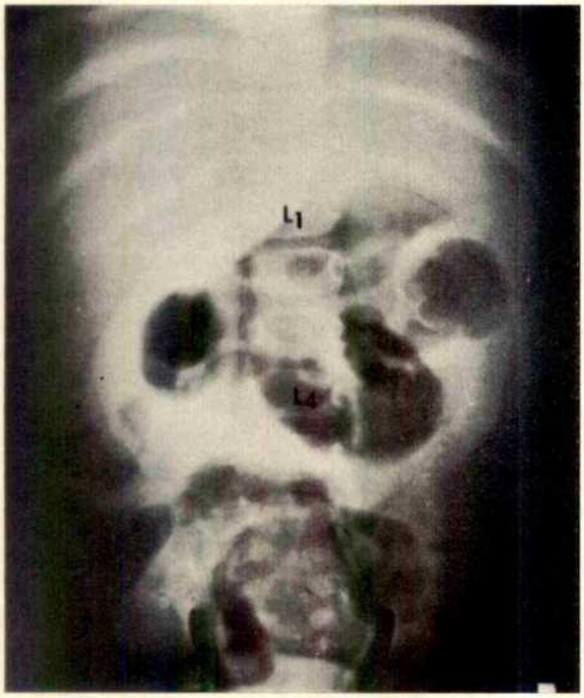


FIG. 7. *Case B.*
Intravenous pyelogram. Normal excretory system. Both kidneys are large with broad parenchyma and smooth borders. No calcifications.

findings may explain the röntgenologic appearance of the large kidneys associated with a normal excretory system (Fig. 7).

In the differential röntgenological diagnosis two major entities must be considered: (1) the non-lipid reticulosis, of which Letter-Siwe disease, which affects the skeleton, lungs and spleen, is the most important; (2) the glucosyl ceramide lipidoses—the Gaucher's disease (Fredrickson and Sloan, 1972a)—of which there are two types: (a) the acute neuronopathic (infantile) type, which does not involve the skeleton because of its rapidly fatal course; and (b) the chronic non-neuronopathic (adult) type which has some röntgenological similarities to N.P.D. Its clinical course is not as stormy as the acute neuronopathic form of N.P.D. and the organ involvement is not as dramatic during the first years of life. Other inborn errors of metabolism which must be considered in the differential diagnosis include the mucopolysaccharidoses and Gm$_1$ gangliosidosis (O'Brien, 1972; Grossman, 1973), Wolman's disease (Neuhauser *et al.*, 1965; Sloan and Fredrickson, 1972) or disseminated lipogranulomatosis (Schanche, 1964). All the above can be ruled out without difficulty if the clinical data and laboratory findings are also taken into consideration when interpreting the röntgenological findings. The large kidneys in the neuronopathic form of N.P.D. deserve special attention since such findings are also seen in lymphoma, glycogen storage disease (von Gierke's disease), bilateral metastases, sickle cell anaemia, nephrosis, polycystic disease or the chronic form of Gaucher's disease (personal observation). These entities may also be accompanied by hepatosplenomegaly.

Although the acute neuronopathic form of N.P.D. is fatal in early infancy, its early diagnosis is of value in genetic counselling. In this respect, the correct interpretation of the röntgenographic changes and confirmation of the diagnosis by enzymatic and histochemical studies is of importance.

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Predictive factors and mechanism of arrhythmias and myocardial ischaemic changes in elderly patients during barium enema

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ABSTRACT

The incidence of significant arrhythmias and ST segment changes during barium enema examination (BE) was evaluated by Holter monitoring of 58 unselected patients over the age of 60 years. Forty percent of the group developed new significant arrhythmias of which the most common were frequent and/or multifocal premature ventricular contractions. Seven percent demonstrated ST segment depression. Administration of glucagon did not diminish the incidence of arrhythmias.

Predictive factors for ECG abnormalities were advancing age, abnormal pre-BE ECG, and pre-BE orthostatic hypotension. Analysis of arrhythmias and response to physiologic manoeuvres suggested that the abnormalities were related to increased sympathetic tone which may be intensified by hypovolaemia resulting from routine bowel preparation.

Patients may develop latent cardiac arrhythmias during the course of routine as well as special diagnostic radiographic procedures (Abrams, 1971; Ansell, 1970; Berg *et al.*, 1973; Berman, *et al.*, 1965; Coskey and Magidson, 1967; Eastwood, 1972). Routine electrocardiographic monitoring during coronary arteriography has revealed electrocardiographic changes ranging from minor repolarization abnormalities to ventricular tachycardia and fibrillation (Coskey and Magidson, 1967; Synder *et al.*, 1971). Recently electrocardiographic monitoring of patients during intravenous pyelography has revealed a high incidence of ventricular premature beats in patients with historical evidence of coronary artery disease (Berg *et al.*, 1973; Stadalnik *et al.*, 1974). Several studies have also indicated a variable incidence of electrocardiographic alterations during procedures which do not involve the use of intravascular contrast agents such as barium enema examinations (Berman *et al.*, 1965; Eastwood, 1972; Stremple and Montgomery, 1961). The data from these studies suggest that significant repolarization abnormalities and arrhythmias are most likely to occur in elderly patients, who are also the group of patients usually requiring barium enema examination.

The current study was designed to: (1) determine the incidence of significant arrhythmias and ST segment depression in elderly patients during barium enema examination; (2) identify those patients at risk during a diagnostic procedure by historical, physiological, and electrocardiographical data; (3) examine the possible ameliorating effects of glucagon which reduces colonic spasm and patient discomfort during barium enema examination (Gohel *et al.*, 1975); and (4) provide insight into the mechanism leading to the electrocardiographic abnormalities.

METHODS

Fifty-eight consecutive patients over the age of 60 years (range 60–98) were selected for Holter monitoring during barium enema examination. Each patient was prepared in the usual manner with laxatives 8–12 hours before and cleansing enemas one to four hours before the examination. The laxatives were X-Prep and two capsules of diocytyl sulfosuccinate. A clear liquid breakfast was given for the evening meal and on the morning of the examination.

Immediately before the barium enema a 12 lead ECG and resting 100 cycle rhythm strip were obtained. In addition, cardiac rhythm was recorded during the Valsalva manoeuvre and during its recovery phase and arterial pressure was measured by cuff sphygmomanometer in the supine and upright positions. During barium enema examination, continuous ECG tape recordings were obtained using a Holter-Avionics Electrocardio-recorder Model 350F. An Avionics Millivolt Calibrator, Model 356A, permitted subsequent analysis of ST segment changes.

Thirty of the patients were randomly chosen to receive glucagon, 1 mg intravenously, immediately preceding the barium enema. During the course of the examination any unusual symptoms or signs were recorded.

Significant new electrocardiographic rhythm disturbances during the barium enema were defined in

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the current study as: atrial tachyarrhythmias consisting of supra-ventricular tachycardia and atrial fibrillation; sinus arrest with escape rhythm or sinus bradycardia; frequent premature ventricular complexes (PVCs) (>7 min or 7/100 cycles); multifocal PVCs; paired PVCs and ventricular tachycardia (Bartel *et al.*, 1974; Kotler *et al.*, 1973). Significant repolarization abnormalities were considered as ST segment depression of greater than 1.0 mV persisting for 80 msec. If the patient had a prior repolarization abnormality on the resting ECG or was being treated with digitalis preparations, then 2.0 mV of additional ST segment depression was required for significance (Bartel *et al.*, 1974).

RESULTS

Incidence of significant electrocardiographic abnormalities

Twenty-seven of the 58 patients (47%) developed significant new electrocardiographic abnormalities during barium enema examination (Fig. 1 and Table I). Twenty-three patients (40%) developed significant arrhythmias and four patients (7%) had significant ST segment depression. Sinus arrest with escape rhythms occurred in 9% of patients while supraventricular tachyarrhythmias were observed in 12% of patients. Ventricular arrhythmias were most frequent; frequent PVCs and multifocal PVCs were observed in 36% and 19% of the group respectively (Figs. 1 and 2). Three patients (5%) actually developed variable periods of ventricular tachycardia during the procedure (Fig. 2); no symptomatic or objective indication of this serious disturbance was observed during the barium study.

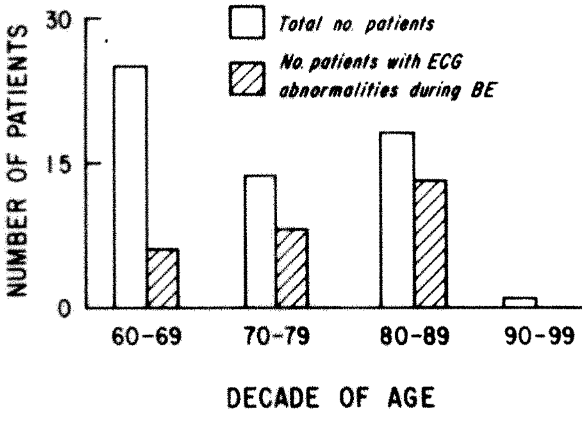

FIG. 1.

Age histogram of patients developing ECG abnormalities during barium enemas

Determination of group at risk during diagnostic procedure

Clinical data: There was a high incidence of abnormalities in patients older than age 60 years (47%). More positive ECGs occurred with each advancing decade of age ($p<0.5$, X^2 analysis) (Fig. 3). Clinical and radiologic evidence of prior heart disease was elicited in 27 of the 58 patients; 15 of these 27 patients developed new ECG abnormalities. This incidence was not significantly greater than in patients without evidence of cardiac disease ($p>0.30$). The incidence of ECG changes was no different in the 17 patients receiving digitalis preparations ($p>0.70$).

Physiological data: 14 of 54 patients in whom systemic arterial pressure was obtained prior to the barium study had a postural fall in systolic pressure of greater than 30 mm Hg or a systolic arterial pressure of less than 90 mm Hg while standing. Eleven of these 14 patients experienced significant ECG abnormalities. Valsalva manoeuvre performed prior to the procedure was not helpful in eliciting or predicting subsequent ECG abnormalities during the procedure.

Electrocardiographic data: The presence of ectopic activity on the 12 lead ECG obtained before the barium enema had a close correlation with the subsequent appearance of a new ventricular arrhythmia during the procedure ($p<0.001$, X^2 analysis). Seventeen of 18 patients with one or more PVCs on the baseline 100 cycle rhythm strip exhibited ventricular arrhythmias during the barium enema, while only four of the patients without PVCs on the baseline strip developed PVCs during the examination. This correlation indicates that the presence of any PVCs on a resting ECG has a highly significant predicative value for significant arrhythmias during

TABLE I

TYPES OF ELECTROCARDIOGRAPHIC ABNORMALITIES IN 58 PATIENTS

	Number of patients
Positive by one abnormality	27
Positive by multiple abnormalities	16
Frequent PVCs	21
Multifocal PVCs	11
Runs of PVCs	10
Ventricular tachycardia	3
Atrial tachycardia	7
Escape rhythms	5
ST segment depression	7

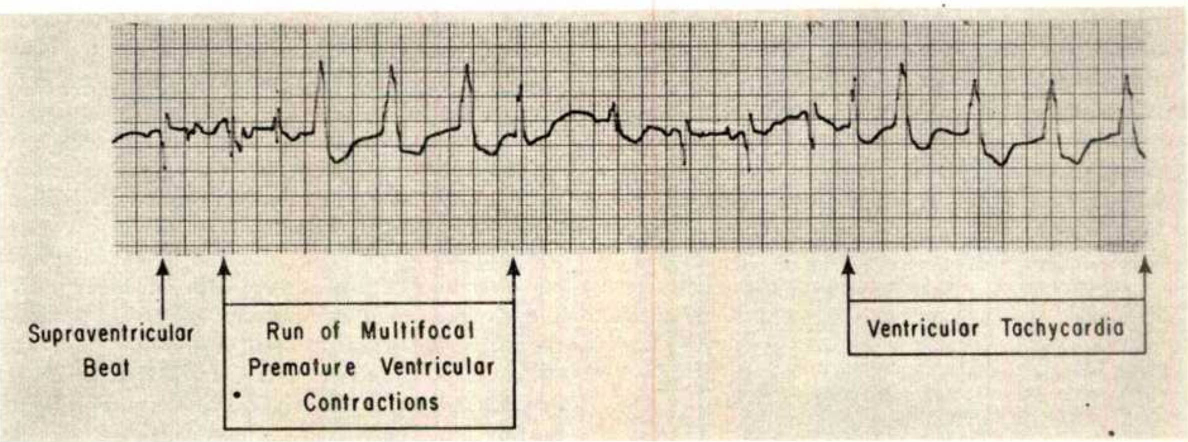

FIG. 2.

Dangerous ventricular arrhythmia during BE. Sixty-three-year-old female with a history of previous Myocardial infarction and occasional PVC's on resting ECG.

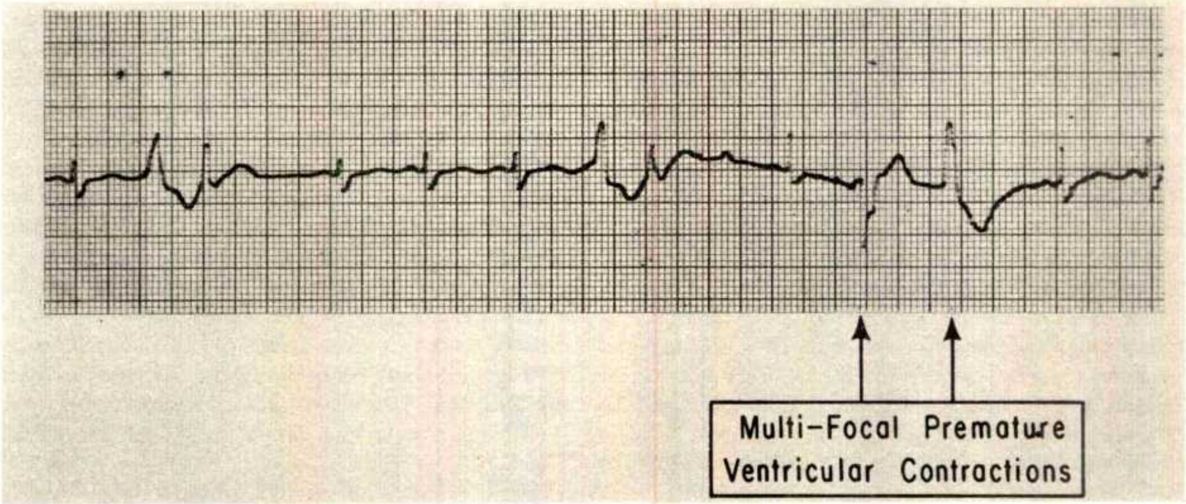

FIG. 3.

Frequent premature ventricular contraction during BE. Eighty-year-old woman without a history of heart disease.

barium enema. Ectopic activity on the baseline ECG was not predicative of ST segment depression.

Effects of prior intravenous administration of glucagon

Ten of the 30 patients who were pre-treated with glucagon developed arrhythmias compared to 11 of 28 who did not receive this agent ($p > 0.70$). The incidence of ST segment changes was not different. Thus, pre-treatment with glucagon in this limited number of patients did not reduce electrocardiographic abnormalities.

Reflex mechanism leading to electrocardiographic abnormalities

Arrhythmias associated with heightened parasympathetic tone, *i.e.*, sinus bradycardia or sinus arrest with escape rhythms (Higgins, *et al.*, 1973; Hockman *et al.*, 1967; Hoffman *et al.*, 1952), were observed in five patients (9%). On the other hand, atrial (supraventricular tachyarrhythmias) and ventricular (frequent PVCs and ventricular tachycardia) arrhythmias, which are more likely to be associated with increased adrenergic neural or humoral stimuli, were elicited in 12% and 36% of the patients respectively. Some patients developed both supra-ventricular tachyarrhythmias and ventricular arrhythmias. Moreover, tachycardia occurred during barium enema examination in 48% of patients who developed ventricular arrhythmias or supraventricular tachycardia, while bradycardia was observed in only 9% of the patients. New ST segment depression was usually observed at heart rates greater than 140 beats/min suggesting increased adrenergic stimulation contributed to ischemic changes as well.

Discussion

Electrocardiographic abnormalities consisting of significant arrhythmias and ST segment depression were elicited in 40% and 7% of 58 elderly patients during the course of routine barium enema examination in the current study. The incidence of ECG changes increased with each advancing decade. Earlier studies evaluating patients of all ages determined an incidence of significant arrhythmias varying from 16% to 21% (Berman *et al.*, 1965; Stadalnik *et al.*, 1974; Stremple and Montgomery, 1961). Analysis of the data from these reports indicates that nearly all patients who developed electrocardiographic abnormalities were older than age 60 years. The most frequent arrhythmias in previous studies as well as the current study were premature ventricular contractions (36%). However, in the current study, more ominous types of ventricular arrhythmias were also frequent, consisting of ventricular tachycardia, multifocal and runs of premature ventricular beats. There were no clinical manifestations of these cardiac arrhythmias and all patients tolerated the barium examination. Despite the occurrence of potentially dangerous cardiac arrhythmias during barium enema examination, shock, sudden death or myocardial infarction has been a rare event (Berman *et al.*, 1965).

Factors which appeared to be associated with and permitted predictability of significant arrhythmias during the examination were advancing age, an abnormal resting ECG obtained prior to the BE and orthostatic hypotension. The correlation with age is demonstrated by the high incidence of arrhythmias in the current study which was restricted to elderly patients and in previous studies performed in patients of all ages in which nearly all arrhythmias occurred in patients older than age 60 years. Furthermore, even in the current study there were proportionally more ECG abnormalities with each advancing decade (Fig. 1) with the exception of the single 90-year-old patient who did not demonstrate any ECG abnormalities. Berg *et al.*, (1973) also found that elderly patients had a considerably higher incidence of ECG abnormalities during intravenous urography.

The finding of any ectopic activity on the baseline ECG exhibited a statistically significant association with the appearance of new ventricular arrhythmia during the BE. While the report of Stremple and Montgomery (1961) also indicated a close correlation between arrhythmia during BE and an initially abnormal ECG, Eastwood, (1972) found the pre-BE ECG of no prognostic value.

Postural hypotension was also related to the subsequent appearance of ECG abnormalities during BE. The postural hypotension is likely due to, or intensified by, the routine preparation of the bowel on the previous night and on the morning of the examination. It appears that the dehydration resulting from routine bowel preparation in elderly patients causes postural hypotension and in some manner promotes the development of arrhythmias during a barium enema.

A history of existing or previous heart disease and response to Valsalva manoeuvre were not reliable predictive factors for the development of ECG abnormalities during BE. The Valsalva manoeuvre, which is operative during evacuation of the bowel, involves variable increases in vagal stimuli to the heart (Berg *et al.*, 1973; Higgins *et al.*, 1973). Some authors have incriminated increased vagal tone in the evaluation of cardiac arrhythmias during BE (Berman *et al.*, 1965; Owen, 1933). However the current study indicates that the Valsalva manoeuvre is not correlated with the appearance of arrhythmias during BE and bradycardia and arrhythmias due to increased vagal tone were not present during BE.

Since it has been clearly demonstrated (Gohel *et al.*, 1975), that glucagon is effective in relaxing the colon during BE and promotes greater patient comfort during the examination, consideration was given to the use of this agent in ameliorating cardiac arrhythmias during BE. In the current study the incidence of ECG abnormalities in those patients pre-treated with glucagon was no different from the untreated patients. On the other hand, pre-treatment with glucagon did not cause any increase in electrocardiographic abnormalities. Thus there does not appear to be any contraindication from the cardiac point of view to the use of glucagon in the elderly patient.

The mechanism responsible for arrhythmias during BE appears to be related to heightened sympathetic tone during BE. Firstly, both atrial and ventricular arrhythmias observed during BE were the type which may be associated with increased adrenergic stimuli to the heart (Hockman *et al.*, 1963; Hoffman, 1967). Secondly, the reflex adjustments to postural hypotension which was closely associated with arrhythmias, has been shown to involve abrupt increases in adrenergic reflex activity and reciprocal decline in para-sympathetic tone (Higgins *et al.*, 1973; Vatner *et al.*, 1974). Thirdly, dehydration, fear and discomfort during the procedure are all factors which stimulate catecholamine release which then increases heart rate and frequency of ectopic heart beats. Furthermore, ST segment depression during BE occurred at heart rates greater than 140 beats/min, again suggesting they were a consequence of adrenergic stimulation. On the other hand, arrhythmias were not specifically related to evacuation of the bowel and the Valsalva manoeuvre performed during the pre-BE ECG did not produce arrhythmias or ST segment changes in patients who subsequently developed these abnormalities during BE. Furthermore, arrhythmias which are potentially mediated by heightened parasympathetic tone (Higgins *et al.*, 1973; Hockman *et al.*, 1967; Hoffman *et al.*, 1952; Hoffman *et al.*, 1967), were infrequently encountered.

In summary, the current study indicates a high incidence of arrhythmias in elderly patients during BE. The potential for developing arrhythmias during diagnostic procedures can be predicted from the resting ECG. The evolution of ECG abnormalities is associated with increased adrenergic cardiac stimulation during BE and may be intensified by dehydration and hypovolemia as a consequence of routine bowel preparation.

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Quantitative aspects of pertechnetate concentration in human parotid and submandibular salivary glands

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ABSTRACT

Quantitative uptakes of ^{99}Tc$^{\mathrm{m}}$-pertechnetate by the salivary glands have been measured in 36 subjects and normal values established. While uptake over the parotid gland increased with time, parotid uptakes were higher at all time intervals than uptakes over the submandibular glands. The uptake over the submandibulars also increased with time. There was no significant difference between resting uptakes of right and left glands, a significant difference would therefore suggest the presence of pathology. Values over the parotid gland are greater under resting conditions than following stimulation, but no such difference was noted for submandibular glands. However, with stimulated glands it was also shown that there was no significant difference between the right and left parotid, or right and left submandibular uptakes. The clinical relevance of these findings is discussed.

Pertechnetate has been shown to be concentrated in human saliva (Harper *et al.*, 1962; Harden and Alexander, 1967; Stephen *et al.*, 1973) and in the salivary glands (Borner *et al.*, 1965; Gates and Work, 1967; Abramson *et al.*, 1969). A technique has been described in which the salivary gland uptake of ^{99}Tc$^{\mathrm{m}}$-pertechnetate can be measured quantitatively by scanning the salivary glands in man (Harden *et al.*, 1967) and we have shown that measurements made using this method agree closely with those made in human biopsy samples (Lazarus *et al.*, 1973). We have suggested that such uptake measurements may be employed as a test of salivary gland function (Stephen *et al.*, 1973). If, however, it is to be used as such, information would be valuable as to the relationship between uptakes in the submandibular and parotid glands on the right and left sides, and the effect of stimulation of the salivary glands with resulting variations in flow rates. In this paper, such quantitative observations are reported in normal subjects.

METHODS

Thirty-six patients without evidence of thyroid gland disease, referred from the Centre for Rheumatic Diseases for routine salivary gland assessment, were studied under resting conditions. There were 25 females and 11 males whose ages ranged from 23 to 78 years, with a mean age of 53 years. One mCi of ^{99}Tc$^{\mathrm{m}}$-pertechnetate was injected intravenously. Using a Selo DS4/4 Superscanner, subjects lay supine on the scanning table, the head being given lateral support by means of an adjustable foam-rubber lined locating device, and were scanned over an area from 1 cm above the bridge of the nose to the cricoid cartilage. As this scanner is a two-headed machine, the response of the system is largely independent of the position of the source, and thus different positions of any gland in subjects will not significantly effect uptake measurements. Scanning was commenced at 1 min, 6 min and 11 min after a tracer dose, each scan taking approximately 4 min. A line spacing of 4 mm and a scan speed of 20 mm per second were used.

An aliquot of the dose solution was scanned under identical conditions after having been placed in a phantom to simulate the salivary glands. The uptake of isotope over the right and left parotid, and the right and left submandibular glands, was quantitated by locating the gland areas on the scintiscans with reference to the anatomical situation of the supine head. A rectangle was then constructed over each gland area, an identical rectangle being taken for each parotid gland region and other similar rectangles for each submandibular gland. In addition, an area representing only blood and natural background radiation was chosen from the supraorbital region. As previously described by Harden *et al.* (1967) and Shimmins *et al.* (1969), the data was displayed on a conventional dot printer and also by a "digital isomap" from the Selo-scanner. The scale factors were adjusted with increasing uptake so that the dot output on the standard printer remained resolvable visually, and the colour-coded numeric scan at no time overflowed. Uptake was expressed as a percentage of the injected dose at the mid-time of each scan.

In six of the above subjects, uptakes over the salivary gland were measured one week later with the salivary glands stimulated. These patients volunteered for this part of the study after being informed of the nature of the procedure, salivary gland dose levels not exceeding 0.5 rem having been approved by the Medical Research Council for patients undergoing repeated research-type studies. Here, acid flavoured candies ("SPANGLES"—Mars Ltd., Slough, England) were crushed and placed in the mouth from one minute before isotope administration until the end of the study. The subject was instructed to suck the stimulant with the minimum amount of mandibular motion. The isotope activity in the "mouth" region was calculated on the scan as the isotope uptake in the area between the parotid and submandibular gland regions.

RESULTS

Comparisons between the right and left parotid and between the right and left submandibular gland uptakes

For all subjects studied, the uptake of $^{99}\mathrm{Tc^mO_4}^-$ by the parotid and submandibular glands was equal to, or greater than, previously determined "normal" values at a mid-scan time of 8 min; mean parotid range: 0.16 – 0.49% dose; mean submandibular range: 0.07 – 0.31% dose (Stephen *et al.*, 1971).

The mean uptakes and range of uptakes over the right and left parotid, and over the right and left submandibular glands expressed as % injected dose at 3, 8 and 15 min are shown in Table I. There was no significant difference between the mean uptake in the right and left glands at any time interval in either the parotid or submandibular glands (as tested by Wilcoxon one-tailed sign ranked test).

There was a highly significant correlation between the uptake over the right parotid gland and the uptake over the left parotid gland at each of the time intervals: at 3 min, $r=0.85$, $P<0.001$, at 8 min, $r=0.84$, $P<0.001$ and at 15 min, $r=0.79$, $P<0.001$. The correlation at 8 min is shown in Fig. 1. The uptake over the right submandibular glands correlated with the uptake over the left glands at 3 min, $r=0.75$, $P<0.001$, at 8 min, $r=0.76$, $P<0.001$ (Fig. 2), and at 13 min, $r=0.77$, $P<0.001$.

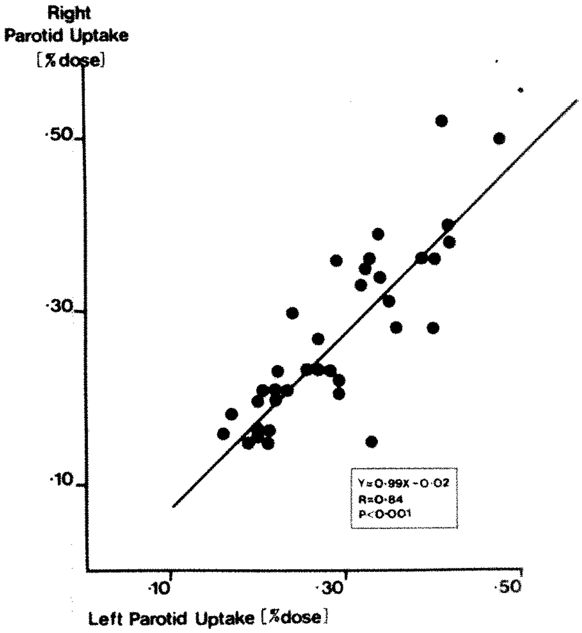

Fig. 1.

Correlation between the right parotid gland uptake and left parotid gland uptake (percent dose $^{99}\mathrm{Tc^m}$-pertechnetate) at a mid-scan time of 8 min in 36 patients.

TABLE I

Uptake and range of uptakes expressed as % injected dose of $^{99}\mathrm{Tc^mO_4}^-$ by parotid and submandibular salivary glands at the mid-scan times of 3, 8, and 13 min (S.E. = Standard Error of Mean).

Time		Parotid			Submandibular		
		Right	Left	Mean	Right	Left	Mean
3 min.	Mean	0.17	0.20	0.19	0.15	0.16	0.15
	S.E.	0.02	0.02	0.02	0.01	0.01	0.01
	Range	0.00–0.36	0.03–0.41	0.02–0.38	0.05–0.25	0.05–0.24	0.05–0.24
8 min.	Mean	0.27	0.29	0.28	0.18	0.18	0.18
	S.E.	0.02	0.01	0.02	0.01	0.01	0.01
	Range	0.16–0.52	0.16–0.48	0.16–0.49	0.08–0.32	0.07–0.32	0.07–0.31
13 min.	Mean	0.29	0.31	0.30	0.17	0.16	0.17
	S.E.	0.02	0.02	0.02	0.01	0.01	0.01
	Range	0.11–0.53	0.13–0.52	0.12–0.51	0.07–0.34	0.08–0.30	0.08–0.31

n = 36)

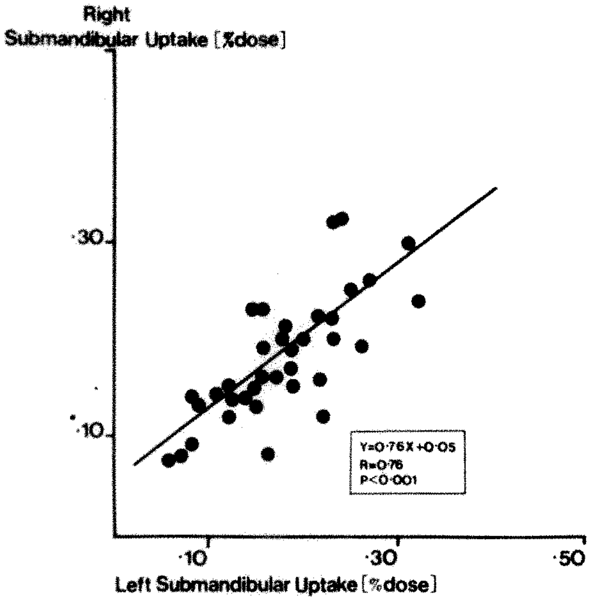

Fig. 2.

Correlation between right submandibular gland uptake and left submandibular gland uptake (percent dose $^{99}Tc^{m}$-pertechnetate) at a mid-scan time of 8 min in 36 patients.

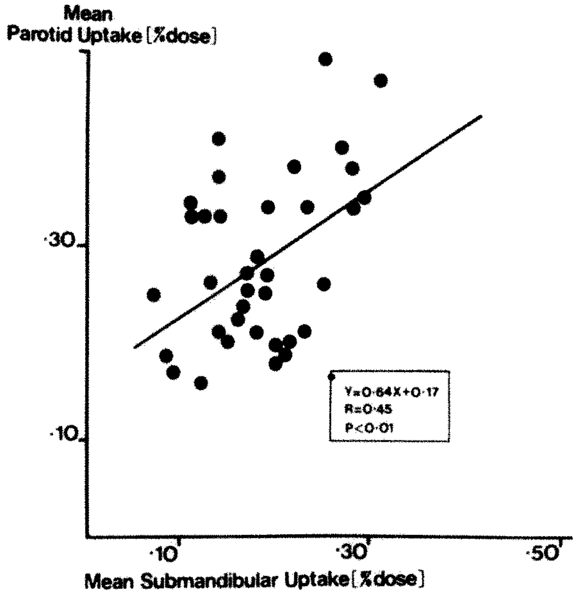

Fig. 3.

Correlation between the mean parotid gland uptake and mean submandibular gland uptake (percent dose $^{99}Tc^{m}$-pertechnetate) at a mid-scan time of 8 min in 36 patients.

Comparisons between parotid and submandibular glands

Comparisons of the mean parotid and submandibular gland uptakes at each of the time intervals indicated in Table I, show that at all times, the parotid gland uptakes were significantly higher than the submandibular uptakes ($P < 0.01$) and this difference was more marked at the later times.

The mean parotid uptake correlated with the mean submandibular uptake: at 3 min, $r = 0.54$, $P < 0.001$, at 8 min, $r = 0.45$, $P < 0.01$ and at 13 min, $r = 0.40$, $P < 0.02$. The values at 8 min are shown in Fig. 3.

Comparisons between salivary gland uptake in resting conditons and following stimulation

For these six subjects, no significant differences were also noted between the mean uptake values of the right and left parotid glands at each of the three time intervals both before, and after stimulation ($P < 0.05$). Likewise, no differences were found between the corresponding submandibular data.

While under resting conditions the parotid gland uptakes increased with time, no such change was noted following stimulation, and at all time intervals, the "resting" values were significantly higher (3 min, $P < 0.05$; 8 min, $P < 0.01$; 13 min, $P < 0.01$). The uptake values over the submandibular gland however, changed little with time or following stimulation (Table II). No significant correlations were established between the mean parotid uptakes before and after stimulation, or between the mean submandibular uptakes under these conditions.

A significant amount of activity was present in the "mouth" region. Under resting conditions, this was least at 3 min and while lower than the 3 min value after stimulation, the difference was not significant. Following stimulation, activity was maximal at 3 min but again resting and stimulated values did not differ significantly at 8 min and 13 min. Here, a significant correlation between pre- and post-stimulation values was only found for the 3 min mid-scan time data ($r = 0.94$, $P < 0.01$).

Discussion

We have shown that the uptake of $^{99}Tc^{m}O_4^-$ by the parotid salivary glands in subjects with no evidence of salivary disease is similar in right and left parotid glands at resting flow rates, and also while the glands were stimulated by sucking crushed candies. A comparable situation has been found with respect to uptakes over right and left submandibular glands. However, while the pattern of uptake over the parotid glands increased with time under resting

TABLE II

MEAN UPTAKE AND RANGE OF UPTAKES, EXPRESSED AS % INJECTED DOSE OF $^{99}\text{Tc}^{m}\text{O}_4^-$ BY PAROTID AND SUBMANDIBULAR SALIVARY GLANDS AND "MOUTH" REGION AT MID-SCAN TIMES OF 3, 8 AND 13 MIN, UNDER RESTING AND STIMULATED FLOW CONDITION. (S.E. = STANDARD ERROR OF MEAN).

Time		Mean parotid		Mean submandibular		Mouth	
		Resting	Following stimulation	Resting	Following stimulation	Resting	Following stimulation
3 min	Mean	0.19	0.16	0.16	0.18	0.69	0.91
	S.E.	0.02	0.02	0.02	0.02	0.09	0.18
	Range	0.14–0.23	0.11–0.22	0.09–0.24	0.09–0.26	0.37–1.05	0.34–1.63
8 min.	Mean	0.28	0.14	0.18	0.14	0.82	0.85
	S.E.	0.02	0.03	0.02	0.01	0.11	0.06
	Range	0.20–0.34	0.06–0.24	0.12–0.28	0.10–0.18	0.36–1.14	0.67–1.05
13 min	Mean	0.29	0.14	0.16	0.15	0.80	0.84
	S.E.	0.02	0.02	0.03	0.02	0.07	0.09
	Range	0.19–0.33	0.08–0.21	0.09–0.31	0.09–0.19	0.53–1.00	0.58–1.21

(n = 6)

conditions, no such change was noted during their repeat period of stimulation. With the submandibular values, resting and stimulated data were not significantly different nor were the uptakes over the "mouth" region.

Parotid resting uptakes are consistently higher than submandibular uptakes, a fact which may be explained by the greater mass and hence greater vascularity of the parotid glands (Testut and Latarjet, 1949).

Although Burgen and Seeman (1957) have shown that in the dog, iodide clearance rose proportionally to the rate of salivary secretion in the stimulated parotid gland, we know that some animal uptakes differ from human uptakes quantitatively (Stephen *et al.*, 1970). In man, quantitative data related to I$^-$, TcO$_4^-$ and other anions have been calculated for saliva with respect to flow rates (Stephen *et al.*, 1973), and we have demonstrated that gland uptakes using scintiscanning, correlate very closely with direct counting of human biopsy material, both for ^{131}I and $^{99}\text{Tc}^{m}\text{O}_4$ (Lazarus *et al.*, 1973). From the data above, it would seem that human parotid gland uptakes are reduced as flow-rates increase, although submandibular values are little affected. The explanation of these gland differences might be related to their capacity to respond to stimulation as the contribution of the parotid glands to the total whole saliva volume is known to increase significantly on stimulation of flow rates, compared with a relative reduction in the contribution from the submandibular glands (Schneyer and Levin, 1955). Therefore, if one assumes that a similar situation exists in the parotid gland as is found with $^{99}\text{Tc}^{m}\text{O}_4^-$ in parotid saliva—*i.e.* a dilution with increased flow effect, any counter-balance by the increase is acinar fluid produced. However, as the flow response of the submanibular gland is proportionally much less, a reduced uptake here under stimulated conditions might not be expected.

While "mouth" values did not differ significantly between "resting" and "stimulated" scans, at the initial scan time of 3 min the "stimulated" value was higher. Previous studies by Harden *et al.* (1967) have shown that "mouth" activity could not be erased by the use of a peschlorate mouth-rinse, but could be delayed by administration of atropine, and it was deduced that most of this activity was due to surface adsorption of isotope on the oral mucosa from the mixed salivary pool. With stimulation, the total mixed salivary volumes will increase rapidly, thus clearing more isotope from the glands in the early stages of the scanning procedure. However, it appears that a plateau level is reached by the 8 min mid-scan time in the stimulated subject. This may be due either to the fact that the whole "mouth" area has by then adsorbed its maximum isotope, or to the increased deglutition rate (in response to the increased salivary flow) clearing more isotope from the "mouth" in a given time, or a combination of both. In the resting group, the lower levels of the "mouth" activity by the 3 min mid-scan time, are presumably due to the reduced volume of mixed saliva which will have carried isotope from glands to the oral cavity by this time. Thereafter this deficiency of fluid will be made up with the resultant increase in oral adsorption of isotope.

In many respects, the thyroid and salivary glands handle pertechnetate similarly, and while it has been suggested by Thompson (1966) that the right lobe of the thyroid gland has a greater uptake of $^{99}\mathrm{Tc^mO_4^-}$ than the left lobe, there is no evidence from the data present to suggest that there is any asymmetry of uptake for either the parotid or submandibular glands. As this equality of uptake for parotids, and for submandibular glands was maintained when saliva was stimulated, any inequality within either of the gland pairs would indicate a pathological process in the gland with the reduced isotope concentration.

As parotid uptake is greater than the submandibular uptake when subjects are un-stimulated, then should the parotid uptake be less than the submandibular uptake at any time interval, again there must be malfunction of one or both parotid glands. The only exception might occur if one encountered a submandibular gland containing a Warthin's tumour, as an excessively high isotope concentration is possible in these cases (Stebner *et al.*, 1968).

While we have shown consistent bilateral results under stimulated conditions, it is only rarely that patients would not be scanned at resting flow rates in the clinical situation. However, if this occurred, it should be borne in mind that the relative parotid values alter compared to the submandibular values as flow rates increase. Therefore, unless one was aware that the patient had been scanned at a stimulated flow-rate, the relatively lower parotid values might be misinterpreted as evidence of a disease process, albeit bilaterally. For best separation of the gland pair data, resting conditions are to be preferred, the mid-scan time of 8 min again providing the earliest opportunity to establish whether or not results correspond to previously determined normal values (Stephen *et al.*, 1971).

The work presented here supplements our previous data (Stephen *et al.*, 1971) and confirms that while other diagnostic procedures exist for assessing salivary gland function clinically, *e.g.* salivary flow studies and sialography, salivary scintiscanning provides a readily available technique of rapidly screening the four major salivary glands simultaneously with the minimum of inconvenience to the patient. Moreover, this can be performed by a scanning technician and does not demand the presence of other trained clinical personnel. Should such screening reveal possible malfunction, the patient may then be referred for further investigations.

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An automatic bolus injector for use in radiotracer studies of blood flow: design and evaluation

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ABSTRACT

An electromechanical device is described which automatically injects the radiotracer bolus used in the measurement of cerebral blood flow. It consists of two electronically controlled, solenoid operated syringes, one containing the radiotracer solution and the other heparinized saline. Results are presented which show that use of the automatic bolus injector in place of hand injection leads to an improvement in the precision of measured flow values. Additional advantages of the device are discussed.

For several years we have measured regional cerebral blood flow (rCBF) in the rhesus monkey using the ^{133}Xe intra-arterial injection technique, wherein the radioactive bolus was injected by hand (Petruk *et al.*, 1974). In these studies, considerable variation in measured flow values under stable physiological conditions was observed.

In this paper we describe an electromechanical device which injects a bolus of ^{133}Xe (dissolved in saline) followed by a heparinized saline flush. Using this device we have found a significant improvement in precision in our rCBF measurements. Additional advantages of the system include: (i) a decrease in experiment duration; (ii) minimal radiation exposure to personnel; and (iii) a reduction in incidence of iatrogenic cerebral air emboli.

MATERIALS AND METHODS

Instrumentation

The main features of the injector system are shown in Fig. 1. Two stainless steel, spring-loaded syringes, one containing the radiotracer solution and the other heparinized saline, are each connected through solenoid operated valves† to an outlet manifold and thereby to the arterial catheter system. The approximate volume of the xenon syringe is 12 ml, the saline syringe 37 ml, and of the manifold and catheter (No. 18 gauge tube 15 cm long) 0.25 ml.

In use, the "xenon valve" (XEV) is programmed to open for a preselected time releasing a small quantity of tracer into the manifold and catheter. Following closure of the xenon valve the "saline flush valve" (SFV) opens for a preselected time flushing residual tracer into the carotid artery.

The electronic control system for the injector is shown schematically in Fig. 2. Following a push-button "inject" command the clock/timer circuits are reset, the XEV armed, and the data acquisition started. After a preset time delay (120 seconds in our experimental studies) during which background measurements are recorded, the XEV is pulsed and a small quantity of tracer introduced into the manifold, catheter and carotid artery. A time delay of 0.1 second is allowed for the XEV to close, after which the SFV is pulsed and the bolus of tracer flushed into the carotid artery. Regular, short pulsing of the SFV prevents clotting at the catheter tip. This "catheter clear" (volume 0.01–0.02 ml) is inhibited during a blood flow measurement. Loading of

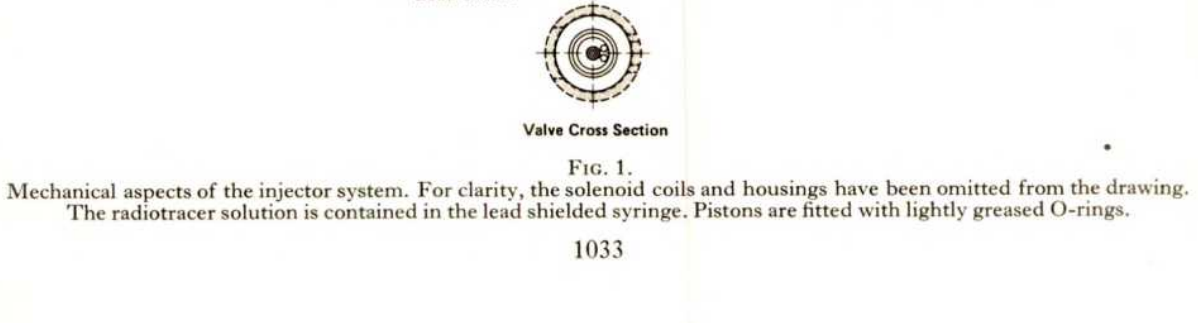

FIG. 1.

Mechanical aspects of the injector system. For clarity, the solenoid coils and housings have been omitted from the drawing. The radiotracer solution is contained in the lead shielded syringe. Pistons are fitted with lightly greased O-rings.

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*Medical Research Council of Canada Fellow.

† ASCO Model 8262B.

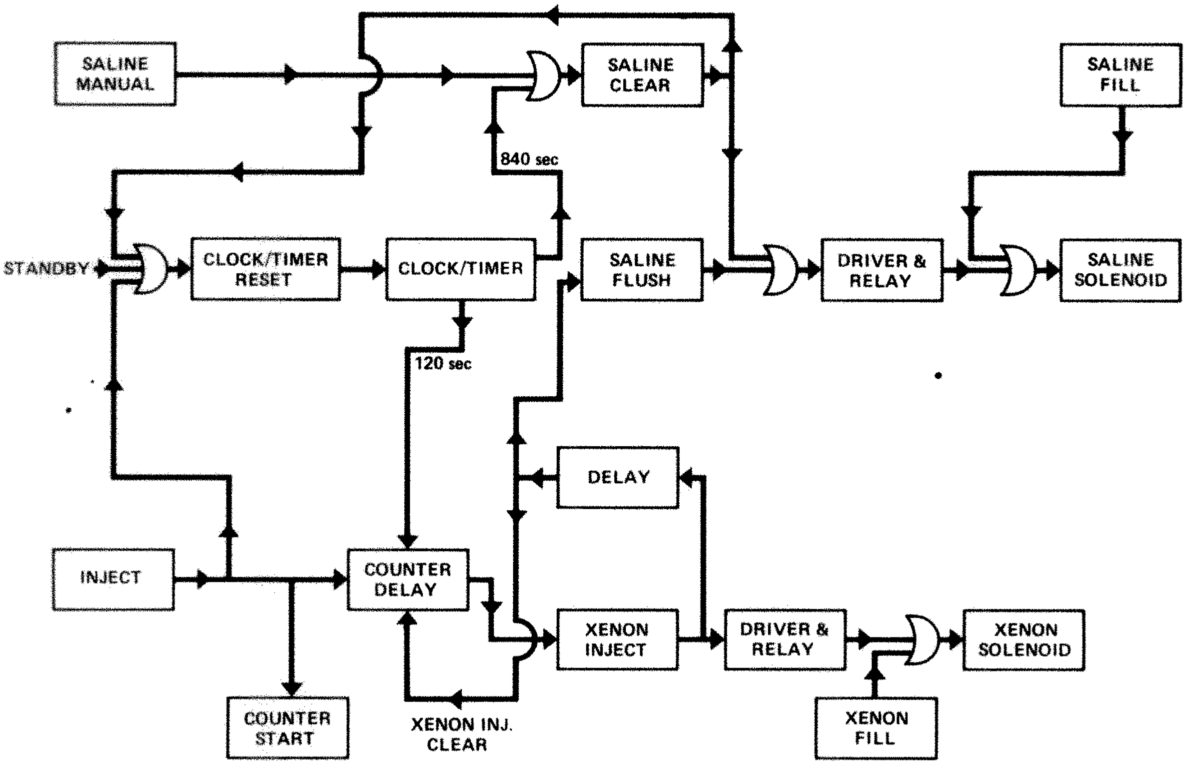

Fig. 2.
Injector control unit.

radio-activity and saline into the syringe system is facilitated by override control (saline fill, xenon fill) of the appropriate solenoid valves.

Experimental procedure

The method of cerebral blood flow measurement using the ^{133}Xe clearance technique has been previously described (Petruk *et al.*, 1973). In the present study, the height/area method of analysis was used to calculate rCBF values for four regions of the brain (frontal, parietal, occipital and temporal) using the data obtained from four small scintillation detectors. In addition, hemispheric blood flow values were measured using a large collimated scintillation detector positioned on the contralateral side of the hemisphere being studied. Flow studies were conducted under stable physiological conditions: arterial blood gases, blood pressure, heart rate, EKG and heamatocrit were monitored in all animals. All rCBF values obtained were normalized to a P_aCO_2 of 40 mm Hg (Hoedt-Rasmussen, 1967).

A standard injection bolus of 3.0 mCi of ^{133}Xe dissolved in 0.5 ml of saline was delivered during 1.2 seconds, followed by a flush of 0.8 ml of heparinized saline delivered in 2.7 seconds.

Three rhesus monkeys were utilized to determine the effect of changes in injection parameters on measured rCBF. In two animals the effect of decreasing the saline volume by 50% or doubling the ^{133}Xe solution volume (while maintaining the quantity of ^{133}Xe fixed) was studied. The third animal was used to determine the relationship between the quantity of ^{133}Xe injected and rCBF; two similar studies were performed over a five hour period.

The rCBF data obtained from these three animal studies were compared with rCBF data obtained from earlier control experiments in three rhesus monkeys. Although performed by a different investigator, these earlier studies were carried out in a manner identical to the present study except that the arterial injections were performed by hand and no attempt was made to control injection parameters. Reproducibility of rCBF values over a four to five hour period was evaluated for each group.

A comparison of hand and automatic injection techniques was carried out with rCBF data from 23

TABLE I

	Frontal	Parietal	Occipital	Temporal	Hemispheric
H	30.9±12.3	25.7±10.2	18.3±9.3	18.8±9.4	18.0±7.8
A	16.8±9.1	11.6±7.7	11.6±10.2	9.4±5.1	9.4±4.4
P	<0.005	<0.001	N.S.	<0.005	<0.005

Mean coefficients of variation (±standard deviation) obtained for four regions of the brain and hemisphere using the hand (H) and the automatic injection (A) techniques. Tests for equality of variance were applied to these data and appropriate "t" tests selected for comparative purposes; results are presented in the bottom row.

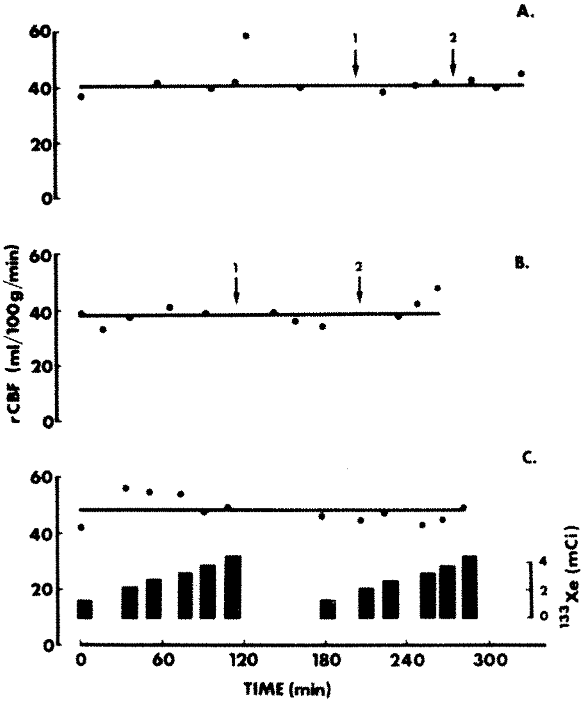

FIG. 3.

Cerebral blood flow values for the parietal region in three rhesus monkeys (see text for details). A and B: arrow 1, flush volume decreased by 50%; arrow 2, flush volume normal, ^{133}Xe solution volume doubled while maintaining injected activity at 3.0 mCi. C: the effect of varying the activity injected while maintaining the specific activity constant at 6.0 mCi/ml. Lines indicate mean of cerebral blood flow values.

rhesus monkeys used in other experiments. In these animals four consecutive baseline rCBF determinations were made prior to altering physiological parameters. In 11 of the animals ^{133}Xe injections were performed by hand and in 12 animals the automatic injector system was utilized. All flow studies in the 23 animals were performed by the same investigator. Reproducibility of the four base-line flow determinations of rCBF values was evaluated for each injection technique.

RESULTS

The effect of altering injection parameters on the measured rCBF values of a single region (parietal) of three rhesus monkeys is shown in Fig. 3. The rCBF values of the remaining regions plus the hemispheric values yielded similar results. Decreasing the saline flush volume by 50% did not produce any significant change in the rCBF values nor did doubling the ^{133}Xe solution volume while maintaining the activity injected at 3.0 mCi. In two studies performed in the same animal (Fig. 3c), rCBF values remained stable over a range of injected activity of 1.0 to 4.0 mCi.

The precision of rCBF measurements in earlier control experiments (hand injections) was compared with similar measurements in the three animals used to study the effects of varying injection parameters. A total of 12 hand injection studies (ten flows per study) of rCBF yielded a mean coefficient of variation (percent standard deviation) of 14.7±5.5 (±S.D.) with a range of 9.3–26.0. Twelve automatic injector studies (11 or 12 flows per study) yielded a mean coefficient of variation of 9.7±3.3 with a range of 5.1–15.2. Thus, a significant improvement ($p<0.025$) in precision was realized using the automatic injector system. Similar results were obtained in a comparison of the reproducibility in four consecutive baseline flow measurements using both hand ($n=11$) and automatic ($n=12$) injection techniques. These data are presented in Table I where the mean coefficient of variation and its standard deviation are shown for the hand (H) and automatic injection (A) measurements obtained from each of the five (four regional and one hemispheric) detectors. It is clear that the mean coefficient of variation is consistently smaller for rCBF measurements using the automatic injector.

DISCUSSION

In addition to an improvement in precision for our rCBF measurements, we believe a number of other important benefits are obtained by using this automatic injector device. For example, following initial connection of the automatic injector manifold to the arterial catheter the fluid-filled system remains closed until the completion of the experimental study. This one-time connection decreases the possibility of introducing air emboli into the brain and also greatly reduces the time required to complete a particular experimental study. Experimental duration is also decreased since preparation of individual tracer injections is avoided and because fewer baseline (control) flows are required.

The reduction in handling of the radioactive material significantly reduces the radiation dose to individuals involved. In a hand injection situation where 15–18 measurements of flow are made during the course of an experimental study, a radiation dose of approximately 20 mR is received by the investigator handling the syringes; this dose is reduced to less than 0.5 mR when using the automatic injection device.

The automatic injector device is portable, inexpensive to manufacture, and has, in our view, led to significant improvements in our experimental methodology. The flexibility provided for in the control of this device also allows investigation of input parameters (bolus shape characterization) and their effect upon measured flow values. This particular modelling study is underway at the present time.

Acknowledgment

The technical assistance of Simon Cox in construction, and of Joan Harvey in evaluation of the device is gratefully acknowledged.

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Report from the Anglo-Dutch study group on thermographic screening. Recommended procedure for breast examination

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For the past two-and-a-half years, several British and Dutch members of the European Thermography Association have been meeting to improve their understanding of various thermographic screening techniques. In particular, the study group has spent considerable time and effort in drafting a recommended procedure for the thermographic examination of the breast. The Anglo-Dutch study group consists of members from a wide variety of disciplines: radiologists, physicists, engineers and surgeons, representing leading centres in the Netherlands and the United Kingdom. It is hoped that the procedures outlined in this report will be adopted as a minimum standard technique, against which all published work should be judged.

RECOMMENDED PROCEDURE FOR THE THERMOGRAPHIC EXAMINATION OF THE BREAST

Patient preparation

The patient's skin must be free from talcum powder, oils or ointments, which affect the emissivity of the skin and lead to artifacts. The patient must be cooled for 15 minutes at 19±1°C with her hands on her hips. There must be no direct draughts on the patient since this may lead to asymmetrical cooling. For most people the thermal pattern will become established within five to ten minutes of disrobing, so that a strict 15 minutes cooling time allows for the worst case. When three changing cubicles are available, 15 minutes causes no delay in the measurement room. A temperature of 19±1°C is considered to minimize interference from cutaneous circulation.

If the patient is cooled in a separate place to the examination room, the patient should then walk through to the examination (also at 19±1°C) with her hands still in position on the hips.

Examination

The examination is made with the hands on the hips. This position is preferred to the hands behind the head position because many patients, particularly the elderly, find it impossible to raise their hands above their shoulders. Since an asymmetrical pattern can be the norm for a particular woman, changes in thermal state are of particular significance as indicators of disease; but to recognize such changes during serial examination demands consistency of procedure, and it is therefore vital that the examination position should always be attainable by the majority of patients.

Patients should be viewed from three positions, anterior, left and right oblique. Care must be taken to ensure that the thermographic camera is properly focused and that there is adequate depth of field. A temperature calibration source must always be included in the field of view and there must be no alteration in the calibration, temperature range, or sensitivity, during the course of the examination. A temperature sensitivity of at least 1°C per scale division is required.

Recording

Special attention should be given to the method of recording the thermographic image for subsequent examination. Monochrome thermograms recorded photographically convey vascular detail but cannot generally be used to record quantitative information unless serial monochromatic isotherms are recorded. Alternatively, quantitative information can be recorded in the form of a colour isothermogram. To avoid loss of information, monochrome thermograms must be recorded on a film having sufficient tonal range. At present this means that only transparency film can be recommended. Recording monochrome thermograms in print form such as the Polaroid Land films is regarded as inadequate. Furthermore, by recording the image on transparency film the opportunity also exists for quantitative measurements using densitometry.

Criteria for the assessment of breast thermographs

From data obtained using the standard procedure just outlined, the Anglo-Dutch study group is endeavouring to relate the degree of thermal abnormality to the probability of breast disease. This will form the basis of a subsequent report. Members of the study group, listed below, are always willing to advise and correspond with persons interested in thermography.

CONTRIBUTORS

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Report from the Anglo-Dutch study group on thermographic screening

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Technical note

The small bowel enema: description and experience of a technique

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ABSTRACT

A method of examining the small bowel, involving duodenal intubation is described. Good visualization of all parts of the small bowel is obtained using an air-barium double contrast technique. The technique is compared and contrasted with the more conventional methods of small bowel examination, and its advantages and disadvantages discussed. The authors relate their experience with the technique, indicating the abnormalities which can be shown, and list the type of clinical problems where the technique may be most usefully employed.

The barium meal and follow-through is still regarded as the conventional method of examining the small bowel, but it is often unsatisfactory, leaving radiologist and clinician uncertain as to the presence, absence or degree of abnormality.

Various techniques have been employed to improve small bowel radiology (Schatski, 1943; Scott Harden, 1960; Laws *et al.*, 1963). This paper is based on the air contrast technique described by Sellink (1971), with minor differences. The technique offers good visualization of all portions of the small bowel, free from overlap, and with sufficient distension of the bowel to show mucosal abnormalities.

THE TECHNIQUE

The patient is prepared as for a barium meal examination. The equipment required is a duodenal tube, a wooden spoon, two 50 ml syringes and a stainless-steel guide-wire. The duodenal tube is made in this department from grey Kifa tubing. It is 110 cm in length and contains eight side-holes within 2 cm of the tip. As the tube is kept coiled, it has a natural curve, and an additional reverse curve is put in about 2 cm from the tip. Initially a straight tube was used, but this often impacted at the apex of the cap. The reverse curve at the end of the tube overcomes this problem.

The tube is passed orally, with the patient's cooperation, into the stomach (8% of patients failed to swallow the tube). It is then manoeuvred into the duodenum, using a stainless-steel guide-wire to give additional rigidity if required. There are two methods of intubating the duodenum using this tube (Figs. 1A and 1B). The ideal position for the tip of

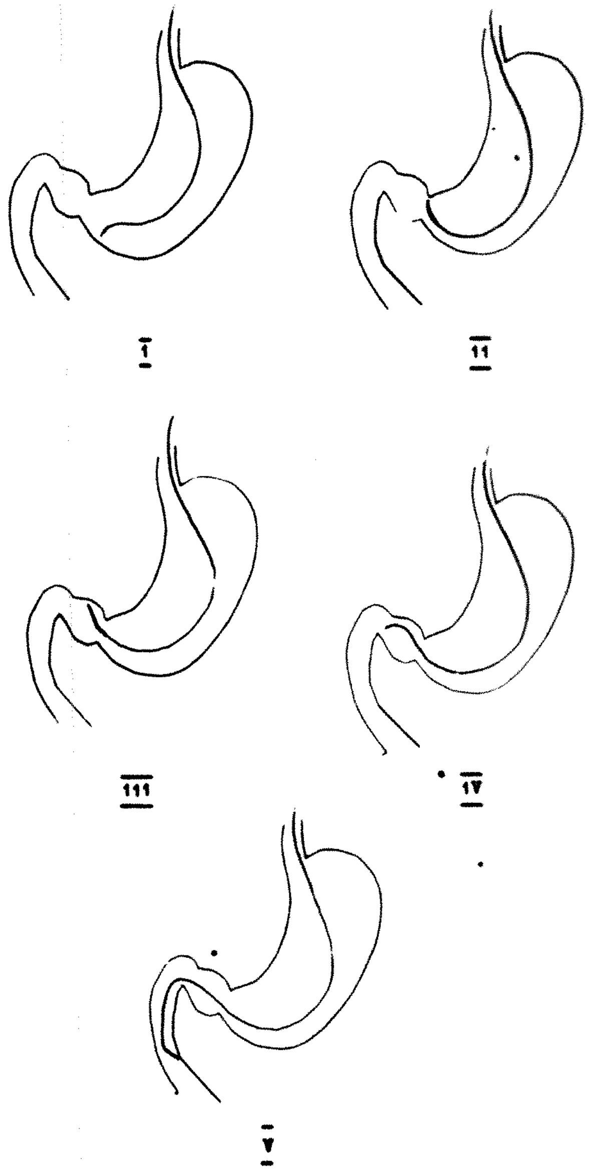

FIG. 1A.

Stage I	Tip of tube in antrum.
Stage II	Rotate tube until tip pointing superiorly.
Stage III	Advance tube into duodenal cap.
Stage IV	Rotate tube until it points inferiorly.
Stage V	Advance tube until tip at junction of 2nd and 3rd parts duodenum.

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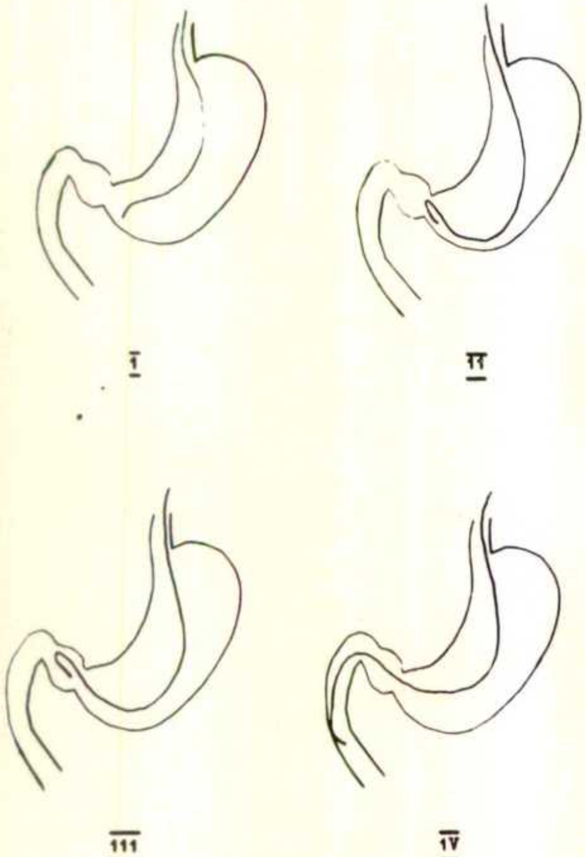

FIG. 1B.

Stage I	Tip in antrum.
Stage II	Advance tube so that reverse bend is accentuated and a narrow U-shaped loop is presented to the pylorus.
Stage III	Advance tube with guide wire inserted and pylorus opens before it.
Stage IV	Advance tube to 2nd and 3rd parts of duodenum.

the tube is at the junction of the second and third parts of the duodenum. Distension of this area with barium induces vigorous peristalsis, which propels the barium caudally (Sellink, 1971).

Micropaque is used, diluted in the ratio of three parts of barium to two of water. This mixture is thin enough to be injected easily through the tube, while retaining good mucosal adherence.

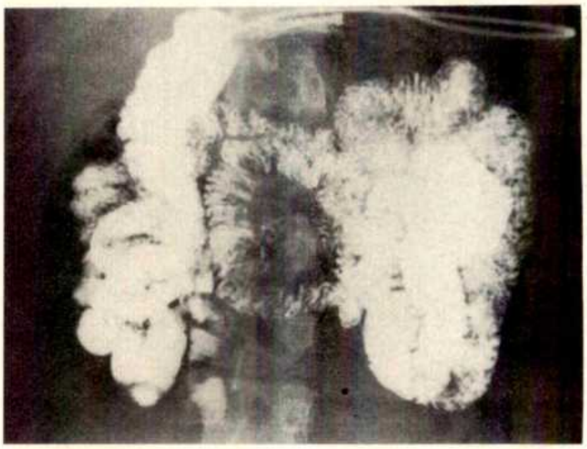

FIG. 2.
Spot film of jejunal loops during barium injection.

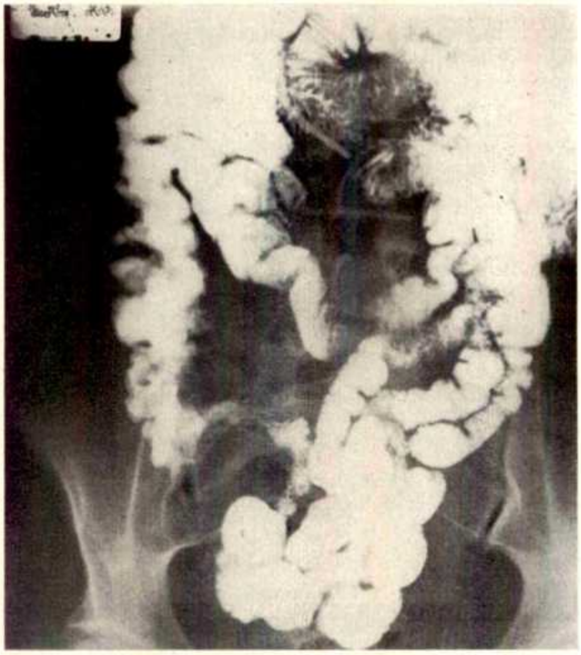

FIG. 3.
Film of the abdomen taken at the end of the injection of barium.

The injection of barium is commenced with the patient supine, to allow easy screening of the abdomen. If reflux occurs into the stomach, the patient is turned into the right lateral position. It then becomes necessary to return the patient to the supine position when screening is required. The rate of injection of the barium is critical, approximately 100 ml/min. A more rapid injection causes reflux, while a slower injection causes insufficient duodenal distension to promote peristalsis. If reflux into the stomach does occur, even with the patient in the right lateral position, and the correct rate of injection, 10 mg Metoclopramide may be given intravenously. However, in this department, this is rarely required. The barium is steadily injected until it reaches the caecum. This usually requires 400–1000 ml of barium, and takes

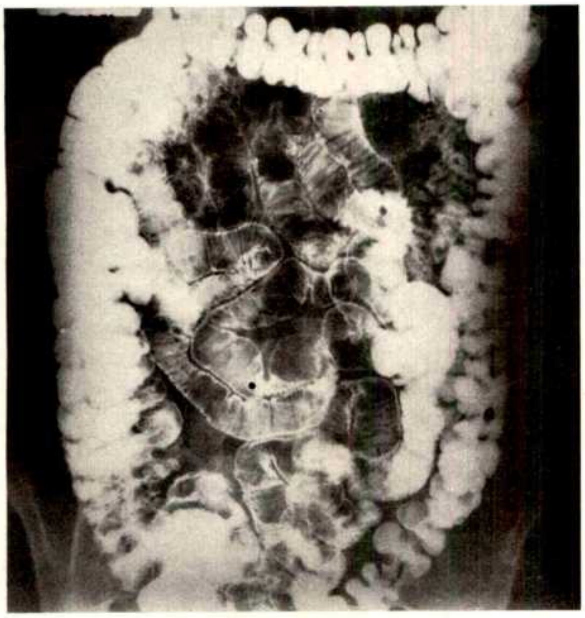

FIG. 4.

Film of the abdomen taken at the end of the air injection.

TABLE I

CONFIRMED PATHOLOGY WAS PRESENT IN 68 CASES (32%)

	No. of cases
Crohn's Disease	36
Adult coeliac disease	7
Adhesions	11
Malignancy	5
Multiple diverticula	5
Malrotation	1
Whipple's Disease	1
Giardia lamblia infestation	1
Anastomotic stricture	1
Total	68

A further two cases had a definite radiological abnormality but the pathology is unconfirmed at the present time.

five to ten minutes. During the injection, intermittent screening of the head of the barium column is performed, and spot films taken with the undercouch tube to show the jejunal loops (Fig. 2). This allows the whole of the small bowel to be examined, minimizing difficulties caused by overlapping loops.

At the end of the barium injection, with the patient supine, the small bowel is carefully examined under the intensifying screen, using the wooden spoon to palpate the abdomen. At this stage, spot films of the terminal ileum are taken, as well as a film of the whole abdomen (Fig. 3).

The patient is now rotated 45 deg. into the right anterior oblique position, and air is injected down the tube. The air passes rapidly through the small bowel, giving a double contrast effect. In all, about 800 ml of air is injected in two to three minutes. Spot films are taken as necessary, and a full abdomen film taken at the end (Fig. 4).

RESULTS

In all, a total of 233 examinations have been attempted. In 19 of these, the patient was unable to swallow the tube, and in a further four patients, duodenal intubation was not successful. Of the 210 successful examinations, 70 were abnormal (Table I). It should be emphasized in interpreting the results, that the cases are selected, being referred for the examination by a clinician interested in gastroenterology, and with a specific problem in mind. All cases have been followed up to the present time (from four-and-a-half years to four months) and so far, no false-negatives or false-positives have been found.

In Table I the statement "Confirmed Pathology" indicates that the diagnosis has been substantiated by surgery, intestinal biopsy or bacteriology.

DISCUSSION

The method described here is almost identical with that introduced by Sellink (1971). The only differences are that in the present study Kifa tubing has been used instead of a Bilbao-Dotter tube and barium has been injected by hand instead of being infused under gravity.

The technique of small bowel enema examination was first described by Schatski (1943). In 1960 Scott Harden recommended intubating the duodenum and injecting 20–30 ml barium diluted with 60–90 ml water followed by up to 300 ml water containing a small amount of magnesium sulphate to avoid absorption of water. The technique is an improvement on conventional methods but is still not ideal as the barium tends to flocculate due to the hyperosmotic magnesium sulphate and the small amount of barium (Sellink, 1970). The water also tends to wash the contrast off the bowel mucosa. Trickey *et al.* (1963) substituted 0.5% methyl cellulose (Prepacol) as the flushing agent but this adds little to the examination and is extremely viscous and difficult to inject. More recently, Pajewski *et al.* (1975) described a double contrast technique giving 200 ml barium followed by air and using intravenous Metoclopramide to stimulate contraction of the bowel.

The main advantages of the double contrast small bowel enema when compared with the conventional follow-through examination are that overlapping loops of bowel can be separated by screening and palpating and that the double contrast effect enhances the demonstration of any abnormality (Fig. 5). In addition, the rapid transit of barium through the bowel prevents flocculation even in patients with coeliac disease (Fig. 6).

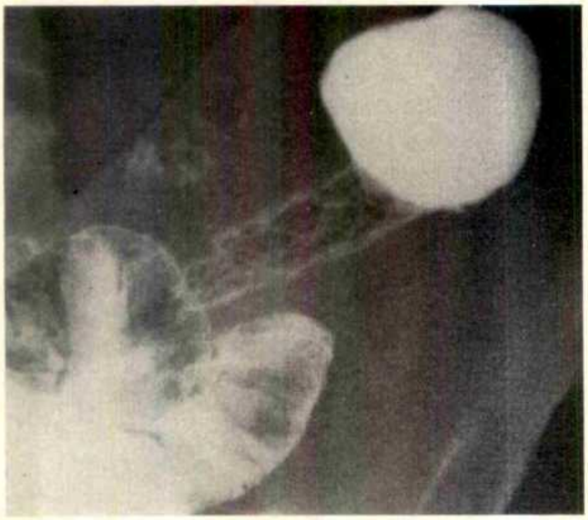

FIG. 5.

Double contrast view of a portion of ileum, showing the cobble-stone mucosal pattern of Crohn's Disease.

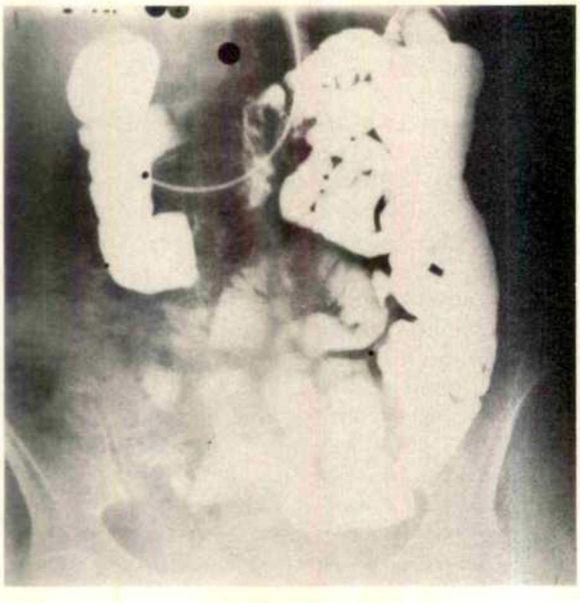

FIG. 6.

Case of adult coeliac disease. The film has been taken during the barium injection phase, and there is no evidence of flocculation. An atrophic mucosal pattern is seen throughout the jejunum.

The disadvantages of the technique are that intubation may be uncomfortable for the patient and that the examination takes, on average, 30 minutes of "radiologist time". It should therefore be reserved for cases where there is a strong suspicion of abnormality or where an answer is required to a specific problem. In our experience the main indications for its use are:

(1) *Crohn's Disease*

This examination has proved not only useful in the diagnosis (Fig. 7), but essential for demonstrating the full extent of lesions in the small bowel, including complications such as fistulae, particularly where surgery is contemplated (Fig. 8).

(2) *Gastrointestinal bleeding*

It is rare for the small bowel to be a source of gastrointestinal bleeding, and this technique should

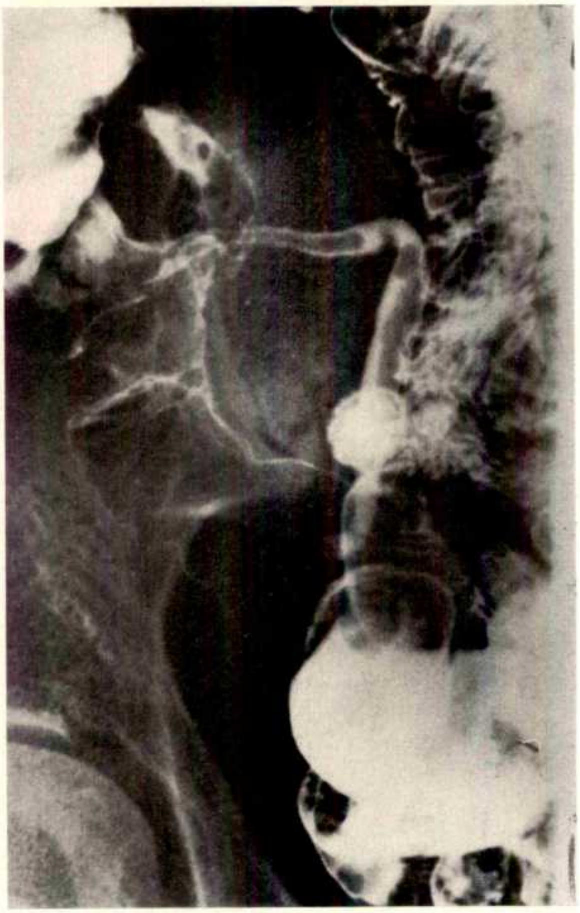

FIG. 7.

Double contrast view of the terminal ileum in a case of Crohn's Disease. The disease was limited to the last two inches of the ileum (surgical proof).

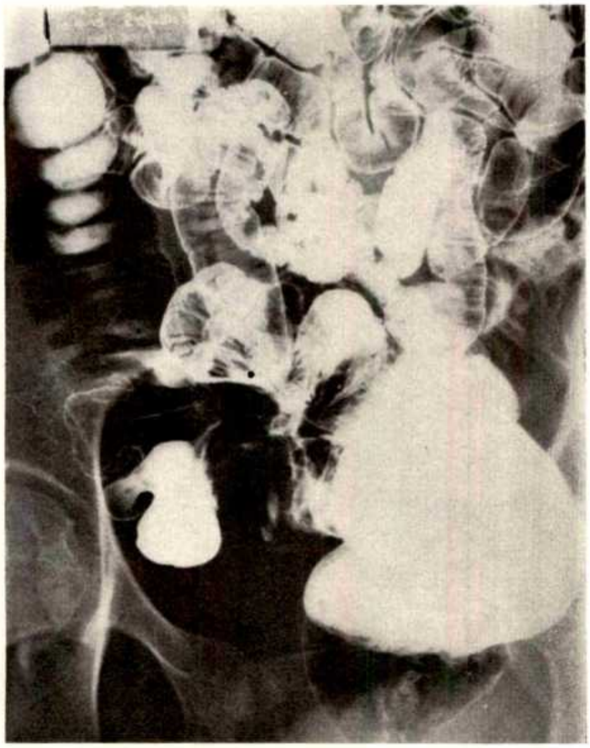

FIG. 8.

Crohn's Disease of terminal ileum, with fistulae into bladder and rectum (surgical proof).

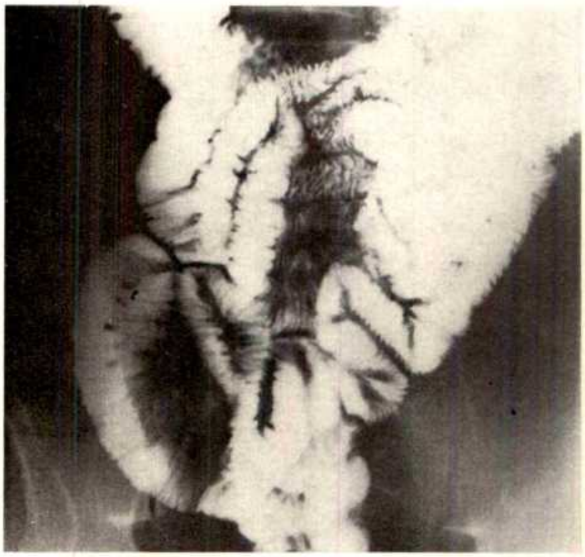

FIG. 9.

Adhesions between loops of jejunum and ileum on the right side of the abdomen, shown during the barium injection phase.

be reserved until other sites of bleeding have been excluded, *i.e.* after barium meal, enema and upper gastrointestinal endoscopy have been negative.

(3) *Malabsorption states*

Intestinal malabsorption is an abnormality of function, best demonstrated by specific tests of absorption.

The place of radiology in this group of diseases is to identify the underlying lesion. The small bowel enema is particularly useful, as flocculation is not a problem, and hence good mucosal detail is obtained.

(4) *Obstructive lesions*

The technique is useful for demonstrating the site and cause of recurrent small bowel obstructions and, in particular, areas of adhesions can be clearly visualized. Adhesion between loops in itself is not significant, but if the bowel shows evidence of kinking, this may be the cause of recurrent obstruction (Fig. 9).

(5) *Other lesions*

There is a further group of patients who are more difficult to define, characterized by general alimentary symptoms, in particular, recurrent abdominal pain and diarrhoea.

Dyer and Dawson (1970) reported a series of 161 cases of Crohn's Disease in whom there had been great variation in the duration of symptoms before the diagnosis was established. In their series, pain and diarrhoea were the most frequent presenting symptoms (occurring in 87% and 66% of patients respectively). They stated that "the low incidence of correct diagnosis is disquieting and is due to factors such as lack of awareness of the condition and failure to perform a barium follow-through examination when both the barium meal and barium enema radiographs are normal".

It is therefore the policy in this department to carry out a small bowel enema in many patients with recurrent diarrhoea and abdominal pain, in order to exclude organic disease. This policy has, of course, led to the higher incidence of negative investigations (Table I) than might otherwise be expected from a highly selected series.

ACKNOWLEDGMENT

We would like to thank Dr. J. R. Bennett for his help in preparing this paper.

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Book review

Fundamental Aspects of Metastasis. Edited by Leonard Weiss, pp. xix+443, 1976 (North-Holland Publishing Company, Amsterdam – Oxford), $53.95.

This book, an expanded version of papers presented at a meeting in Buffalo last July, has appeared with commendable speed; and it covers much of the ground implied in its title.

A good deal of attention is devoted to biophysical changes in the surface of neoplastic cells, but it is clear that the appraisal of such changes is still immensely difficult. What, for example, is their specificity? And how do they actually contribute to the phenotypic traits of invasiveness and metastasis? Subtle variations in membrane structure rather than gross abnormalities seem to be involved, and current investigations appear to be moving towards the study of topographical redistribution components in and on the cell surface. More details of some of the techniques used in such work would have been helpful. Biophysical aspects of contact phenomena—between individual tumour cells and between tumour cells and endothelium—are discussed. Even though simplified *in vitro* models are used, the results are complex and hard to evaluate.

Among the chapters devoted to *in vivo* studies of experimental metastasis, there is an excellent account of the morphological changes associated with the escape of tumour cells through vessel walls. The authors conclude that "The tumour does not vacate the vessel, it destroys it". Several papers are devoted to the localization of metastatic tumour, and there is a resurgence of interest in the contribution made by the disseminating tumour cells themselves: it is possible that some tumour cells may carry tissue specific surface determinants. The "soil" aspects of Paget's familiar "seed and soil" analogy for metastatic growth is dealt with somewhat perfunctorily. Immunological factors which may impinge on the metastatic process—mainly in determining which shed tumour cells develop into metastatic foci—are reviewed in three chapters. Surprisingly, this section contains no adequate discussion of lymph node changes in animals (or people) with metastasising tumours, and the more general question of lymphatic spread is virtually ignored.

The final section, on metastasis in man, is less satisfactory. There is no account, for example, of the cell kinetics of metastatic tumours, and the chapters on techniques for detecting and monitoring metastases by physical and biological methods contain little that is new.

In summary, a well-documented and up-to-date book which brings together a large mass of scattered facts. There are certain omissions, and some aspects of the subject are more adequately presented than others. Much of the work described here has, as yet, few direct implications for the practising oncologist, but it provides a stimulating account of a lot of work that is going on in this crucial, but extraordinarily ill-understood, aspect of malignant disease.

RICHARD CARTER.

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Case report

Diagnosis of splenic torsion: a combined radiographic approach

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(*Received February, 1976*)

Torsion of the spleen about its pedicle is a rare condition in North America and Europe, comprising only 0.2% of splenectomies performed at the Mayo Clinic between 1904 and 1945 (Pugh, 1946). In underdeveloped nations the rate of occurrence is probably slightly higher due to the increased presence of splenomegaly secondary to malnutrition and malaria (Cross, 1974; Carswell, 1974).

Although this event is seldom suspected preoperatively, a thorough radiographic evaluation may be useful. This report will describe an approach to the correct diagnosis employing barium studies, diagnostic ultrasound, nuclear medicine and angiography. By utilizing all of these procedures, a specific diagnosis may be possible.

CASE REPORT

A 26-year-old white female was hospitalized for evaluation of severe left upper abdominal pain of one week's duration. The patient had a three-year history of mild intermittent abdominal pain, exacerbated by blunt trauma. Physical examination revealed a tender left upper quadrant abdominal mass, but was otherwise entirely normal. Her temperature was 38.9°C. Laboratory data included a white count of 15000 with a slightly elevated serum amylase and LDH. No other abnormal laboratory studies were noted. A plain film of the abdomen revealed a large homogeneous left upper quadrant mass, without calcification, depressing the colonic bowel gas inferiorly. Excretory urography suggested an extrarenal left upper quadrant mass, while an upper gastrointestinal study demonstrated a retrogastric mass (Fig. 1). Diagnostic ultrasound examination showed a well-defined sonolucent mass, consistent with an enlarged spleen (Fig. 2). A liver scintiphoto study, employing ^{99}Tc^{m} sulphur colloid, revealed a normal liver with absence of splenic activity. The suggested diagnosis was an enlarged spleen, with vascular compromise to this organ. A subsequent coeliac arteriogram demonstrated abrupt interruption of the splenic artery (Fig. 3). Either splenic torsion or splenic pedicle trauma without torsion was thought to be the most likely diagnosis. At laparotomy, a massively enlarged spleen with 360 deg. torsion of the splenic pedicle was encountered. There was absence of normal splenorenal ligaments. Microscopic sections revealed widespread haemorrhage consistent with prolonged venous obstruction.

DISCUSSION

Torsion of the spleen represents a varied degree of rotation of this organ on its pedicle, with secondary vascular compromise. It is generally thought that the spleen may be subject to torsion because of incomplete fusion of the posterior mesogastrium in the embryo, with the result that the lienorenal ligament and occasionally the phrenicocolic ligament fail to develop (Woodward, 1967). Other proposed causes, including splenomegaly and trauma, are probably only secondary factors acting upon an already abnormal embryonic development of the ligaments. The splenomegaly associated with this entity in North America and Europe is usually secondary to venous obstruction with delayed complete arterial

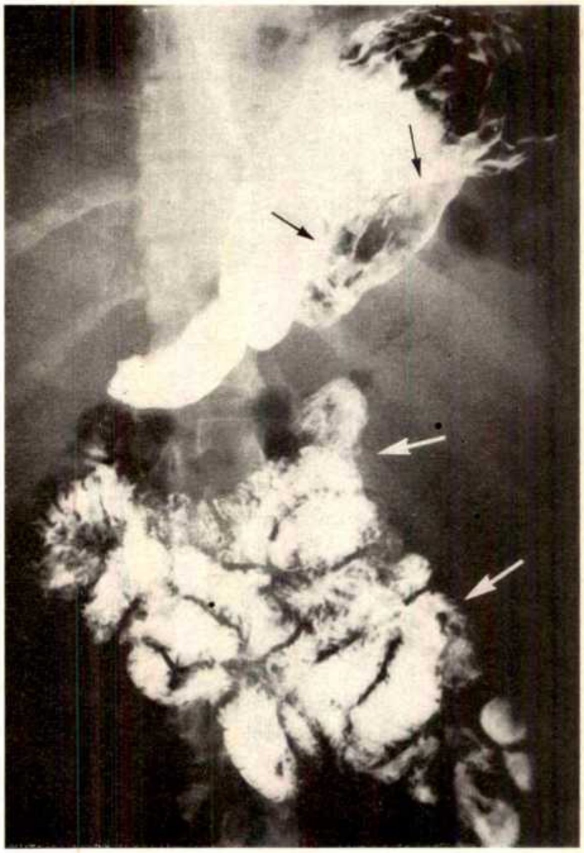

FIG. 1.

Upper gastrointestinal series, prone position. A large left upper quadrant mass elevates the barium-filled stomach (black arrows), and depresses loops of small bowel (white arrows).

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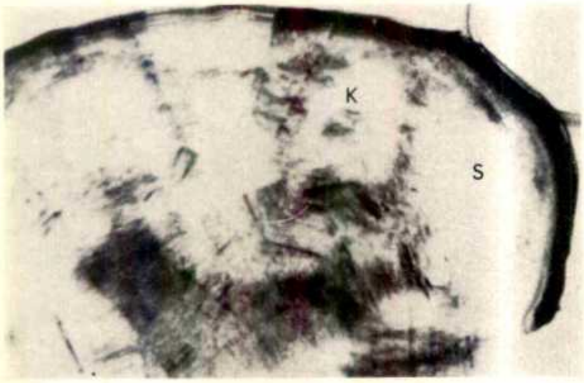

FIG. 2.

Ultrasound B mode, upper abdominal prone transverse section. The enlarged spleen (S) is shown in relationship to the normal left kidney (K).

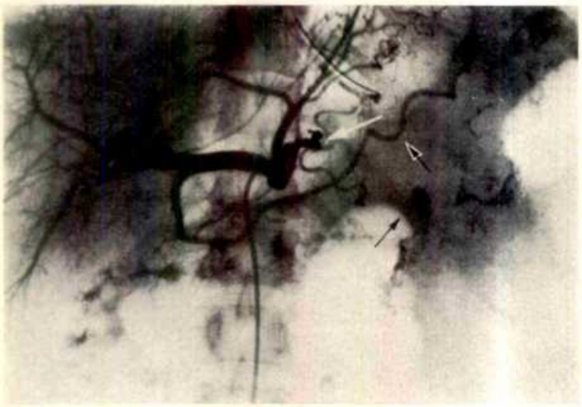

FIG. 3.

Coeliac arteriogram, arterial phase, subtraction study. There is an abrupt termination of the distorted splenic artery (white arrow), with elevation of the gastro-epiploic artery (black arrow, white border) by the enlarged spleen. Densities produced by residual colonic barium (black arrow) are seen below the gastro-epiploic artery.

compromise. In under-developed countries, malnutrition and malaria represent the most common causes of splenomegaly.

Torsion of the spleen may present with non-specific clinical findings, including symptoms of acute cholecystitis, appendicitis or peritonitis (Darle *et al.*, 1967; DeBartolo *et al.*, 1973), acute abdominal pain and left upper quadrant mass following trauma (Rosenthall *et al.*, 1974), and chronic hypersplenism (Weinreb *et al.*, 1974). Because of the varied clinical manifestations and rarity of this condition, the pre-operative diagnosis is seldom made. Especially in countries where splenomegaly is not commonly seen, the diagnosis may be missed. Barium studies may define the size and configuration of the left upper quadrant mass, and radioisotope and angiographic studies may further define the vascular abnormalities. This case is the first reported in which diagnostic ultrasound was used as an additional diagnostic method. The ultrasound study was useful in characterizing the left upper quadrant mass as an enlarged spleen.

In rare cases, the early stages of sickle cell anaemia may present with splenomegaly and the absence of radioisotopic visualization of the spleen (Spencer *et al.*, 1970). However, the clinical history will often differentiate this entity from torsion of the spleen. Angiographically, torsion of the spleen might be expected to produce a tapered splenic artery, as opposed to a more abrupt termination associated with thromboembolic entities, such as sickle cell disease. However, this former finding was not demonstrated in this case.

In conclusion, this report presents a case of torsion of the spleen with demonstration of the value of various imaging techniques for making a correct diagnosis. Despite the rarity of the condition and the varied clinical manifestations, correct diagnosis should be possible with thorough radiological study.

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(The Editors do not hold themselves responsible for opinions expressed by correspondents)

THE EDITOR—SIR,

CALIFORNIUM-252 IN RADIOTHERAPY: RBE–DOSE RATE RELATIONSHIPS

In a recent article on the potential of Californium-252 in radiotherapy (Hall and Rossi, 1975) the authors reviewed the experimental, physical and biological work that has been done up to 1974. They observed that the RBE values of Cf neutrons relative to γ rays tend to scatter around a common line which indicates a decrease in RBE as a function of increasing dose rate. RBE values for several biological systems such as cells cultured *in vitro*, pig skin, mouse jejunum, lymphocytic leukaemia cells and mouse lethality, appear to show the same relationship as a function of dose rate. The authors also mentioned that the fit is not perfect because of the well-known RBE variations among different tissues and cell systems. The few points some distance from the line were discussed in more detail and an explanation was provided.

With respect to this RBE versus dose-rate relationship, it is of interest to make a few comments:

(1) a closer look at the data of Fairchild *et al.* (1970) and Hall *et al.* (1974) provides RBE values somewhat lower than the RBE values quoted in the review article mentioned. Fairchild *et al.* (1970) exposed HeLa cells to $\mathrm{Cf}(n+\gamma)$ radiation. The γ-ray component of the $\mathrm{Cf}(n+\gamma)$ radiation was 37 per cent. D_0 values of survival curves obtained were 71 rad for the $\mathrm{Cf}(n+\gamma)$ radiation at 16 rad/h and 200 rad for the protracted γ radiation. Hence, the RBE as the ratio of the D_0 values is 2.8. When a correction is made for the γ-ray contribution according to the formula

$$\frac{1}{D_{0(n+\gamma)}} = \frac{F_n}{D_{0(n)}} + \frac{F_\gamma}{D_{0(\gamma)}}$$

in which F_n and F_γ are the fractions of the total absorbed dose delivered by neutrons and gamma rays respectively (Hall, 1972), the RBE calculated is 3.9. This value is also quoted in a review article of Atkins *et al.* (1973) while in Hall and Rossi's article (1975) this RBE was calculated as 5. In the paper by Hall *et al.* (1974), V79 Chinese hamster cells cultured *in vitro* were used to compare radium γ rays with the mixed neutron/γ ray emission from Cf at a dose rate of 18 rad/h. The RBE derived from survival curves was 3.5; when corrected for the γ contribution the RBE of the neutron component alone was about 5.9. However, when the same calculation is made for the neutron RBE as mentioned above, the RBE obtained is 4.7. The recalculated RBE values are included in Fig. 1, points F and H2 respectively.

(2) Additional data points available in the literature which are not included in the RBE-dose rate relationship make this relationship much more complex. Hall (1972) used Chinese hamster cells and exposed them to $\mathrm{Cf}(n+\gamma)$ radiation at dose rates between 1.14 and 21.4 rad/h and to low dose-rate γ rays. The RBE calculated for Cf neutrons compared with γ rays at 35.7 rad/h is 6.7. When the same overall time is taken for both the gamma exposure and the Cf exposure to obtain the same survival level, the Cf dose rate is 5.3 rad/h. This RBE value of 6.7 at a dose rate of 5.3 rad/h, not included in Hall and Rossi's RBE-dose rate relationship, is presented in Fig. 1, point H1. In the report of Atkins *et al.* (1973), an RBE of Cf neutrons of 2.44 at a dose rate of 10.8 rad/h was reported for effects on the hemopoietic system as studied by Carsten, point C(A2) in Fig. 1. Furthermore, in the same paper, RBE values of 4.38 for HeLa cells at a dose rate of 13 rad/h and of 3.94 for hamster cells at 13.5 rad/h were quoted. These RBE values are also included in Fig. 1, points A2.

(3) RBE values of fast neutrons at low dose rates for effects on tumours must be significantly larger than RBE values obtained for normal tissues in order to achieve a therapeutic advantage. Therefore, in order to predict a therapeutic advantage, it is necessary to analyse in detail differences between responses of malignant and normal tissues and in vitro systems to radiation. This has already been done for RBE values as a function of dose or dose per fraction for acute fast neutron irradiation (Barendsen, 1971). Atkins *et al.* (1973) observed that the RBE values of Cf neutrons for effects on single cells were smaller than the RBE values for effects on normal tissues in the clinically interesting range of dose rates of 30–50 rad/h for the standard gamma radiation. The data obtained by Fu *et al.* (1974) do indeed indicate that the RBE for the mouse EMT-6 tumour system is larger than that for normal tissue systems, point F1, Fig. 1. This observation agrees well with that of Kal (1974) and Kal *et al.* (1974), that the RBE of 15 MeV (DT) neutrons at 48 rad/h for the rat rhabdomyosarcoma was larger than that for the rat skin, *i.e.* 4.3 and 2.7 respectively. For a comparison with RBE values for Cf neutrons, a factor of about 1.85 for the differences in the energy dissipation patterns of 15 MeV and Cf neutrons must be taken into account (Broerse *et al.*, 1968). The extrapolated RBE values obtained for effects on tumour and skin are 7.7 and 5, points K1 and K2, Fig. 1, respectively.

In Fig. 1, the most relevant data to date are summarised. Excluded are data points obtained for *Vicia faba* (Hall and Fairchild, 1970) and for hamster cells (Nias *et al.*, 1973), for reasons mentioned earlier (Hall and Rossi, 1975). It might be deduced that in the range of dose rates of 6 to 60 rad/h an RBE-dose rate relationship for normal tissues can be distinguished as indicated by the dashed line in Fig. 1. This line is fitted through the data points according to the least squares method. In this dose-rate range the published RBE values for cell cultures *in vitro* as well as for bone marrow cells used in the spleen colony assay indicated by the open circles are smaller than corresponding RBE values for normal tissues. However, the two RBE values for tumour systems, data points F1 and K1 in Fig. 1 are larger than those for normal tissues; this indicates that a clinical evaluation for the utilization of Cf neutrons in radiotherapy is worthwhile and promising.

Yours, etc.,
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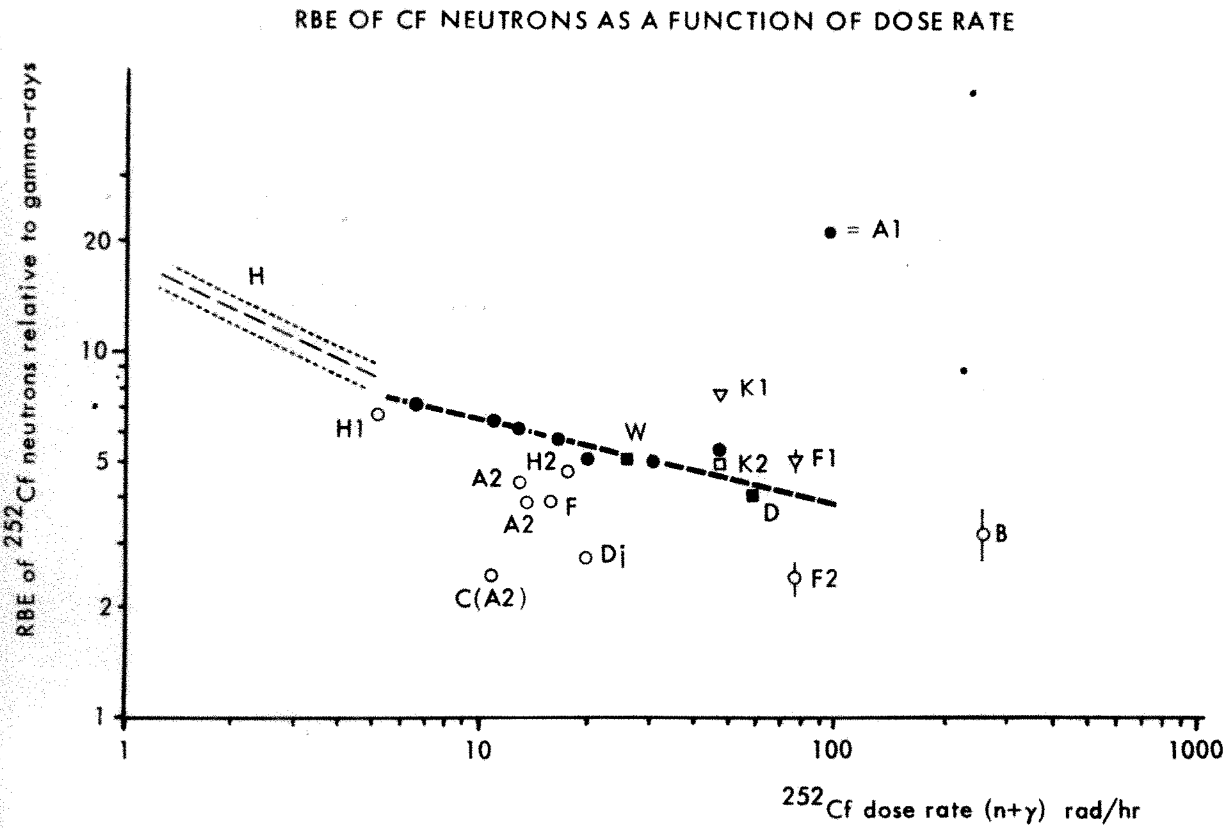

FIG. 1.

RBE of ^{252}Cf neutrons relative to γ rays as a function of ^{252}Cf absorbed $(n+\gamma)$ dose rate. The letters represent the following studies:

A1 : Pig skin, Atkins *et al.*, 1972.
A2 : HeLa and Chinese hamster cells, Atkins *et al.*, 1973.
B : P-388 cells, Berry *et al.*, 1973.
C(A2) : haemopoietic system, Carsten, see Atkins *et al.*, 1973.
D : mouse $LD_{50/30}$, Dean *et al.*, 1972.
Dj : HeLa cells, Djordjevic *et al.*, 1973.
F : HeLa cells, Fairchild *et al.*, 1970.
F1 and F2 : mouse EMT-6 tumour and bone marrow respectively, Fu *et al.*, 1974.
H : proliferation of Chinese hamster cells, Hall *et al.*, 1971.
H1 : Chinese hamster cells, Hall, 1972.
H2 : V-79 cells, Hall *et al.*, 1974.
K1 : rat rhabdomyosarcoma, Kal, 1974, Kal *et al.*, 1974 (extrapolated value).
K2 : rat skin, Kal, 1974, Kal *et al.*, 1974 (extrapolated value).
W : jejunal crypt cells, Withers *et al.*, 1971.

The dashed line is fitted through the data points A1, D and W according to the least squares method.

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THE EDITOR—SIR,

CALIFORNIUM-252 IN RADIOTHERAPY: RBE-DOSE RATE RELATIONSHIPS

We are grateful to Dr. Kal for his courtesy in showing us a preprint of his letter (Kal, 1976), which comments on our recent review paper (Hall and Rossi, 1975), and giving us this opportunity to reply.

It would appear that Dr. Kal has applied corrections to only some of the data and that a consistent application of the corrections would not support his thesis. In particular there are three points that we would like to make by way of reply.

(1) Dr. Kal has revised downwards the RBE estimates for cell culture systems by applying the exact formula, which he graciously attributes to one of us (E.J.H.), to allow for the γ contribution. He does not, however, apply the same formula to the pig skin data of Atkins *et al.* (1972), because of course the parameters are simply not known. Atkins *et al.* (1972) calculated RBE values for californium neutrons by using the approximate formula:

$$\text{RBE} = \frac{\text{D}\gamma\ \text{cesium or radium} - \text{D}\gamma\ \text{californium}}{\text{Dn californium}}$$

If this method of calculating RBE's is applied to (for example) point H_1, it moves up from 6.7 to 7.7 and then falls exactly in the same line as the pig skin data. This contradicts Dr. Kal's argument that normal tissues give RBE's larger than in vitro cultures.

(2) Dr. Kal speaks of "normal tissues" as a group but in the figure draws a line which is a least square fit only to pig skin, mouse gut colonies and $\text{LD}_{50/30}$ data. Why does he not include points C and F_2, which relate to CFU in the mouse spleen? Are not these normal tissues? It could be argued that they are not dose-limiting in radiotherapy, but then neither are the critical cells that lead to the $\text{LD}_{50/30}$ assay (point D).

(3) The most important conclusions of Dr. Kal's letter is that the neutron RBE for tumours is larger than for normal tissues, hence making neutrons look very attractive. In the case of ^{252}Cf this is based solely on the EMT 6 data of Fu *et al.* (1974). In these experiments, ^{252}Cf at a dose rate of 80 rad/h was compared with γ rays at 270 rad/h. This is a very high dose rate, far higher than is used clinically for ^{252}Cf implants, and as a consequence the treatment time was short. It is not surprising that under these conditions neutrons are more effective than γ-rays since there is no opportunity for hypoxic cells to reoxygenate during treatment, as they most certainly would for a continuous low dose-rate or a fractionated treatment regimen. To draw far-reaching conclusions from these data is very misleading.

Dr. Kal's final conclusion that a clinical evaluation of ^{252}Cf in radiotherapy is worthwhile and promising may well be true. But the arguments that lead to it in the letter cannot be adduced from the data under consideration. We would reiterate the points made in our review paper (Hall and Rossi, 1975) which we believe represent a more conservative interpretation of the collected literature.

(i) In general the RBE of ^{252}Cf neutrons relative to γ-rays tends to fall as the dose-rate increases.

(ii) At any given dose-rate, the RBE varies significantly with the biological system or endpoint studied. We suggest that RBE values are *big* for biological systems which show a large capacity to accumulate and repair sub-lethal damage (big shoulder on the acute X-ray survival curve) and *small* for biological systems which show little accumulation and repair of sublethal damage (small shoulder on the acute X-ray survival curve). In our view, the data do not warrant any other generalizations. Specifically they do not warrant the conclusion that RBE's for tumours are always higher than for normal tissues, nor that cells cultured *in vitro* always give rise to smaller RBE's than systems involving normal tissues.

Yours etc.,

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THE EDITOR—SIR,

THE OER AT LOW DOSE-RATES

Interest in the treatment of human cancers with beam therapy at low dose-rates, with fractionation using multiple doses per day (Pierquin *et al.*, 1974; Brown *et al.*, 1974) and with the utilization of ^{252}Cf neutrons at low dose-rates (Hall and Rossi, 1975) is steadily growing. Studies performed with experimental tumours indicate that low dose-rate irradiation and multifractionation might be quite efficient because reoxygenation of severely hypoxic cells, redistribution of cells over the cell cycle with a relatively larger fraction of cells in the G_2 phase (Kal and Barendsen, 1972) and absence of repopulation due to a short overall time of treatment partly balance repair of sublethal damage.

Neary (1955) indicated that the OER for *Vicia faba* at low dose-rates was between 1.3 and 2. Hall *et al.* (1966) reported that the OER for HeLa cells was 1.5 at 32 rad/h and Hall and Cavanagh (1967) determined for *Vicia faba* an OER of 2.06 at 19°C and 2.7 at 3°C at a dose-rate of 46.3 rad/h.

These data prompted Withers and Chen (1971) to suggest that γ rays at low dose-rates could be considered as "poor man's neutrons". At international congresses during the past few years we gained the impression from radiotherapists that the OER is indeed not considered to play the same role at low dose-rates that it does at high dose-rates; in other words, the OER at low dose-rates is considered to be smaller than the OER at high dose-rates which is in the range 2.5–3 for most mammalian cell lines.

Recent publications on the OER of ^{252}Cf neutrons, and Ra γ-rays at low dose-rates have shown, however, that the OER values for several biological systems are between 2.0 and 2.7. Their mean value is about 20% lower than the mean OER value obtained at high dose-rates (Atkins *et al.*, 1973; Berry, 1968; Berry *et al.*, 1973; Bushong *et al.*, 1973;

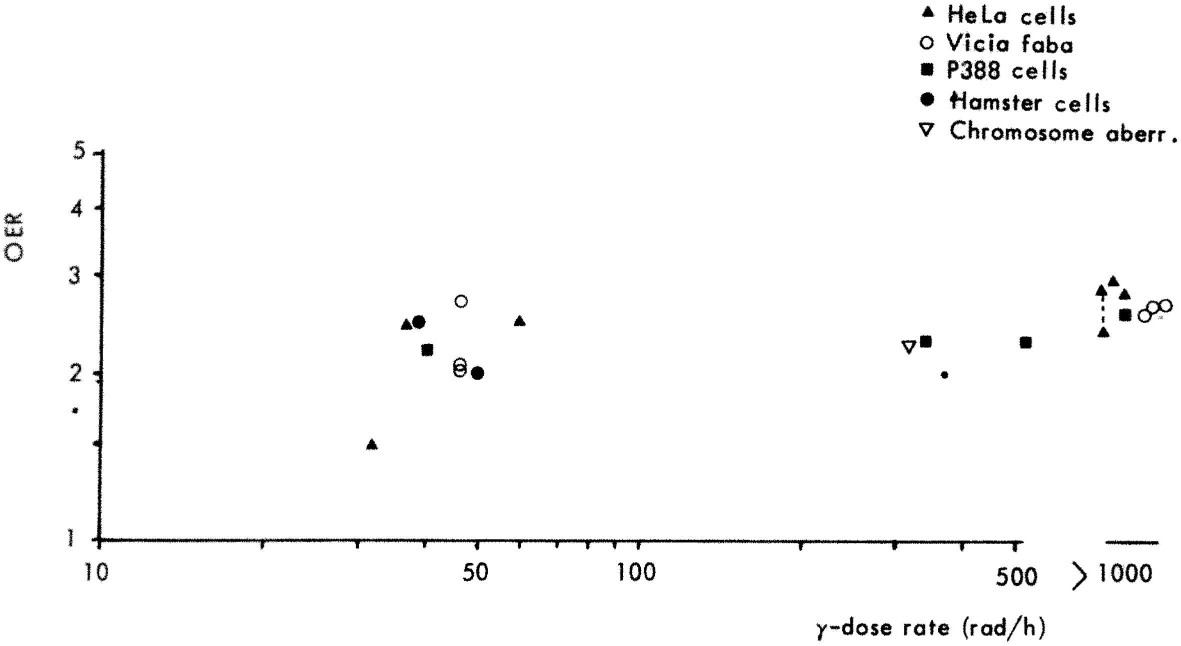

FIG. 1.

Oxygen enhancement ratios as a function of γ dose-rate for several biological systems: *Vicia faba* (Hall and Cavanagh, 1967; Hall and Fairchild, 1970), HeLa cells (Hall *et al.*, 1966; Drew *et al.*, 1972; Djordjevic *et al.*, 1973), P388 cells (Berry, 1968; Berry *et al.*, 1973), hamster cells (Atkins *et al.*, 1973; Hall *et al.*, 1974) and chromosome aberrations (Bushong *et al.*, 1973).

Djordjevic *et al.*, 1973; Drew *et al.*, 1972; Hall and Fairchild, 1970; Hall *et al.*, 1974). We have plotted in Fig. 1 the OER values as a function of dose-rate for the various test systems. These data show that the OER is almost independent of dose-rate and that the low OER values quoted by Neary (1955) and Hall *et al.* (1966) are significantly lower than the other reported values.

It is our opinion that, in general, the reported OER values are subject to criticism. The determination of OER values at low dose-rates inevitably involves technical difficulties. The test system must be maintained under hypoxic conditions for long periods of time. This represents a serious difficulty when working with most biological materials, *e.g.* it has been shown that the cloning efficiency of cells stored under anoxic conditions to serve as a control for the cells irradiated under the same conditions decreases considerably as a function of storage time. This indicates that cells are damaged by this treatment alone. It is quite possible that the damage induced by this anoxic storage may result in a more than additive effect when those cells are irradiated. Therefore, to obtain more realistic OER values, cells irradiated at high dose-rates in air as well as those irradiated under anoxic conditions should have had a pre-treatment period of storage under anoxic conditions which is comparable with the storage times of the cells irradiated at low dose-rates. The result may well be that the difference of about 20% in OER values obtained at low dose-rates as compared with OER values obtained at high dose-rates as shown in Fig. 1 will not be observed if the cells to be irradiated in air at high dose-rates are pre-treated under hypoxic conditions.

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Proceedings of The British Institute of Radiology

Abstracts of papers read at the Thirty-Fourth Annual Congress, April 8–9, 1976 held at University College, Gower Street, London WC1*

New diagnostic imaging techniques

Chairman: Professor J. R. Mallard

Computer subtraction of CT scans in clinical use and calculations of regional cerebral blood volume, by E. Zilkha, G. Ladurner, L. D. Iliff, L. E. Claveria, J. Marshall and G. H. du Boulay.
Spin mapping, by E. R. Andrew, W. S. Hinshaw and W. S. Moore.
The zone plate camera—a circular tour of coded aperture imaging, by D. R. Dance, Adèle Nicholas, R. P. Parker, S. Webb and B. C. Wilson.
A Compton effect gamma camera, by J. S. Fleming, D. B. Everett, J. M. Nightingale and R. W. Todd.
Preliminary study of the use of a gamma camera to measure body sections from Compton scatter, by G. Harding.
Two stage photographic harmonization and its applications, by B. S. Worthington.

COMPUTER SUBTRACTION OF CT SCANS IN CLINICAL USE AND CALCULATION OF REGIONAL CEREBRAL BLOOD VOLUME

By E. Zilkha, G. Ladurner, L. D. Iliff,
L. E. Claveria, J. Marshall and G. H. Du Boulay

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A method for measuring regional cerebral blood volume (rCBV) using the EMI-scanner was described. A group of 13 patients had brain scans prior to, and immediately following, the intravenous injection of sodium iothalamate (1.75 ml/kg).

Blood samples taken before the administration of sodium iothalamate and at the beginning and end of the second scan were scanned in a skull phantom to obtain the increase in EMI number caused by the presence of the contrast material in the blood.

A computer was then used to subtract the two brain scans and display the result as a picture on an oscilloscope display. The computer was also used to calculate the mean changes in EMI number in various regions of the brain which, together with the values obtained for the blood, were used to calculate the percentage of blood in the brain (CBV).

Significant regional differences in CBV were obtained, values in the frontal and temporal regions being lower than the hemisphere mean (4.9 ± 0.7), while being higher in the occipital region. The left, dominant hemisphere had a significantly higher CBV than the right hemisphere.

CBV in the cortex, at 6.0 ± 1.8, was significantly higher than the hemisphere mean but showed no regional pattern.

SPIN MAPPING

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Spin mapping is a method of image formation based on nuclear magnetic resonance (NMR) and belongs to a new class of methods sometimes called Zeugmatography. In spin mapping the specimen of interest is placed in a magnetic field typically 0.1 to 1 tesla, and is subjected to three orthogonal alternating magnetic field gradients applied at low asynchronous frequencies. The proton NMR signal from the specimen is taken through a low pass filter which rejects all except the signal from a small volume element at the intersection of the three orthogonal null planes of the three alternating gradients. This sensitive volume element is scanned by raster through sections of the object, mapping out a three-dimensional image of proton spin density in the specimen.

The feasibility of the method has been established with small specimens of order 1 cm size using a conventional NMR spectrometer. Specimens have included inanimate structures and biological specimens, for example a spring onion and a chicken bone. Resolution was about 0.3 mm in all three directions. Differences of nuclear relaxation times in parts of the specimen could be discriminated and mapped, and may aid in distinguishing cancerous tissue.

The work is being extended to objects of larger size and to human subjects. The method is non-invasive and is believed to involve no human hazard. A feature of the technique is the ability to "focus down" on a smaller region of the specimen and re-examine it in greater detail, or to halt the scan and examine at one point in the specimen such NMR characteristics as relaxation time, flow, diffusion and resonance shift. Imaging times are substantially reduced by a technique for multiple sensitive point scanning.

THE ZONE PLATE CAMERA—A CIRCULAR TOUR OF CODED APERTURE IMAGING

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Coded apertures are an alternative to the conventional collimators used in radiosiotope imaging. They have a high sensitivity and produce a coded image which contains information about the three-dimensional activity distribution within the object. This image must be unscrambled to recover the original distribution.

Following Barrett (1972) we have used a zone plate as a coded aperture. The images thus obtained have been successfully decoded both digitally (Wilson *et al.*, 1975) and optically (Nicholas and Parker, 1976).

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The gain in sensitivity of the zone plate over a conventional collimator can be a factor of 1000, making the gamma-camera unsuitable as a detector due to its count rate limitations. However, film is a viable alternative. When imaging in two dimensions the Poissonian noise increases with the size of the reconstructed image and for film it is necessary to demagnify the image to obtain a reasonable signal to noise ratio. For large objects it is also necessary to increase the exposure time. Such a zone-plate-film camera could have a resolution of 2 cm and a field of view 150 cm square. It would be lightweight and portable and would cost just a few hundred pounds.

Statistical fluctuations are also a limitation in three dimensional imaging. The only artefact free reconstruction technique we have found requires an image with 5×10^{10} counts. Such statistics cannot be obtained by imaging *in vivo* radionuclides.

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A COMPTON EFFECT GAMMA CAMERA

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A novel design of gamma camera using the Compton effect is described. The energy loss and three-dimensional position of successive Compton collisions in a detector are recorded. Calculations using these data allow constraints to be put on the probable direction of the incident photons without using a collimator. The information from a large number of photons allows an image of a distribution of isotope to be built up.

Since no collimator is required the potential image resolution and sensitivity of this system are not limited by this factor as are most present imaging devices. Computer simulations show that image resolutions should be as good as the best of present gamma cameras and the sensitivity a factor of ten better. It has the additional advantages that the upper limit of usable energy is considerably higher than with present systems and that tomographic images focused at any selected plane in the patient's body can be obtained by simply varying an electronic parameter.

The preferred form of detector is considered to consist of a number of thin two-dimensional position sensitive semiconductor detectors stacked on top of one another. A prototype detector consisting of two such detector slices made using the gold n-silicon surface barrier mechanism is currently being constructed. Measurements on the performance of the individual slices in terms of energy and position resolution show that the image resolution of the prototype system should be comparable with current imaging devices.

PRELIMINARY STUDY OF THE USE OF A GAMMA CAMERA TO MEASURE BODY SECTIONS FROM COMPTON SCATTER

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The possibility has been examined of imaging body cross-sections by detection of Compton scattered radiation using a gamma camera. In comparison with the focused crystal detector generally used in previous scatter measurements, the gamma camera has a superior sensitivity-resolution product, and by combining energy and position resolution, facilitates discrimination against photons which do not originate in single scattering of the primary beam.

Measurements have been made of the scatter produced by a well-collimated beam of 0.66 MeV γ rays, derived from a 20 Ci^{137}Cs source, interacting with anatomical phantoms and a human subject. The system allows 10% counting statistics, sufficient to resolve the differences in electron density between air, water and bone, to be accumulated in a scan time of two minutes. A serious shortcoming of the cross-sections obtained, however, is their non-uniformity owing to attenuation of both the primary and secondary radiations.

Although it has been shown, in the case of a scanning focused detector, that such non-uniformity may be reduced using two opposed sources and bilateral detection (Tothill, 1975), the expense of such an arrangement in the present case would be excessive.

An alternative approach has been implemented in which the data is corrected by computation of the primary and scatter radiation attenuation factors over the cross-section. A cross-section through the chest of a human volunteer has been obtained with this arrangement. The results show some promise and proposals for further improvement of the technique are outlined.

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TWO STAGE PHOTOGRAPHIC HARMONIZATION AND ITS APPLICATIONS

By B. S. Worthington

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Harmonization of a radiograph involves a transformation of the image whereby the overall background or macro-contrast is diminished whilst that of fine detail in the image is preserved.

A blurred positive mask is made from the original film by diffusing the image through a thin sheet of opal Perspex on to an unexposed film placed underneath. The image so produced lacks the detail of the original, registering only the background or macro-contrast. By combining this mask and the original film part of the background is cancelled out with consequent subjective enhancement of detail. On harmonized copies there is invariably a better rendering of the detail of any soft tissues which is substantially due to a reduction in the tonal range of densities particularly in regions of high density on the original film.

A second stage has been added to the method, which consists of combining the harmonized copy with the original film, thus restoring the background contrast to normal, but the detail is now, as it were, represented twice and the detail contrast is increased; therefore, at a given spacing of detail elements their perceptibility will be greatly enhanced.

Joint radiotherapy/radiobiology session

Chairman: Dr. J. R. Fowler

Existing time-dose formulae and some of their limitations, by W. E. Liversage and J. S. Orr
Repair and the radiotherapist, by N. M. Bleehen
Fractionated radiotherapy and cell kinetics, by Julianna Denekamp
Time in fractionated radiotherapy, by V. H. J. Svoboda
A comparative trial of large and small fractions, by J. M. Henk and K. W. James

EXISTING TIME-DOSE FORMULAE AND SOME OF THEIR LIMITATIONS

By W. E. Liversage
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Strandqvist (1944) found that the iso-effect curve for skin tolerance had a slope of 0.22 whilst Cohen (1960) found a slope of 0.33. Despite this apparent difference, their clinical data and the data of Fowler (1965) are in excellent agreement provided the latter are assumed to apply to treatments given at five fractions per week and the same definition of overall time is applied to all three sets of data. Over the range five to 25 fractions these data disagree with the Ellis NSD formula (Ellis, 1967; 1968) by as much as 20 or 25%. The TDF system of Orton and Ellis (1973) and the CRE system of Kirk *et al.* (1971) are based on this simple formula which implies that:

Iso-effect dose = Constant $\times N^{A} \times T^{B}$

where N is the number of fractions and T is the overall time.

Radiobiological work has been stimulated by the introduction of the NSD concept and attempts have been made to determine the values of the "constants" A and B for different tissues. This work suggests that A is a function of T and B is a function of N (Liversage, 1973; Hopewell and Berry, 1975). If T is kept small, A decreases as N increases (Dutreix *et al.*, 1973; Douglas *et al.*, 1975). If N is large, B increases as T increases (Liversage, 1973).

In the case of rapidly proliferating tissues, these findings suggest that the iso-effect dose should rise rapidly at first, due to intracellular recovery, then rise relatively slowly and finally rise very steeply due to repopulation, as the number of daily fractions is increased, *i.e.* the shape of the iso-effect curve should be similar to that found by Paterson (1948) for skin tolerance involving régimes up to 50 fractions in ten weeks.

Methods of improving the accuracy of our existing dose-time relationships are needed.

At least two systems of time-dose formulae have now been developed which are based explicitly on scales which describe the states to which normal tissue is brought by radiation, and in which a single number is assumed to describe completely the state of the tissue. These two systems, the CRE system (Kirk *et al.*, 1971; 1972) and the TDF factor system (Orton and Ellis, 1973), are based on equivalent scales on which equivalent points are connected by a constant simple relationship. Further, the scales are quite different from the scale concept used in the NSD system (Ellis, 1968). This clarification of the scale has been an important step.

Despite the fact that the CRE and TDF factor systems present equivalent solutions to ordinary problems associated with fractionated régimes of treatment, they have different approaches to two other common clinical problems. These are (a) the combination of fractionated treatments with continuous irradiation treatments, in which the TDF system fails to provide a volume correction factor; and (b) the corrections to be made to scale values for gaps in treatment, for which Orton and Ellis used an inappropriate power and incorporated overall time of treatment in the correction.

The careful study of these two problems in the clinical situation will help to illuminate the approximations inherent in the fractionation formulae, and together with radiobiological studies, guide the improvements in the system. The drive for improvement shows that the present time-dose formulae have real clinical value, despite their current limitations.

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REPAIR AND THE RADIOTHERAPIST

By N. M. Bleehen

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The significance of sublethal or potentially lethal damage following radiation or drug treatment of cancer was discussed. Repair of sublethal radiation damage has been well documented as has its importance in fractionated radiotherapy régimes. Less well documented has been the importance of recovery from potentially lethal damage. This phenomenon has been described for radiation *in vitro* and in experimental tumour systems *in vivo*. Further types of slow recovery from radiation damage have also been described in the capillaries and in lungs. The various conditions under which recovery from potentially lethal radiation and drug damage may occur were described, together with possible methods of modifying this recovery by drugs and hyperthermia. However, unless repair inhibitors selectively acting on tumour rather than normal tissue cells can be found, there will be little advantage, and indeed possibly major disadvantages, in the employment of such techniques.

FRACTIONATED RADIOTHERAPY AND CELL KINETICS

By Julianna Denekamp

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Radiation can perturb the cell proliferation kinetics of a population, and the cell kinetics themselves influence the response of the cell population to any dose of radiation. These two areas of interaction are of importance in the response of tumours and normal tissues to fractionated irradiation. The influence of cell kinetic parameters on the processes occurring between fractions was discussed, *viz.* repair, redistribution, reoxygenation and repopulation.

Although no differences in the extent of repair of sublethal injury could be predicted from kinetic parameters, certain tumours have been shown to have a lower repair capacity than normal tissues. Cells which are in the non-growth-fraction or which are hypoxic may have a reduced ability to repair sublethal or potentially lethal damage. Rapidly dividing cells are unlikely to exhibit slow repair, which may be the important time component in fractionated radiotherapy.

Cells in certain phases of the cell cycle are more sensitive to radiation and are more readily killed, leaving a partially synchronised population whose sensitivity will change as it becomes redistributed around the cell cycle. Although the potential exists for using this difference in sensitivities to increase the therapeutic gain, the information necessary to plan such a strategy is formidable and is unlikely to be available using current techniques.

Reoxygenation of previously hypoxic cells has been shown to occur in six different tumours. This reoxygenation is more extensive in the three carcinomas than in the sarcoma. It is postulated that this results from different shrinkage rates occurring after irradiation, which in turn relates to the cell loss factor, being high in the rapidly shrinking carcinomas.

Accelerated repopulation occurs in normal tissues in response to cell depletion. A similar rapid proliferation may also occur in certain animal tumours. The onset of more rapid proliferation is early in the intestine, delayed for one to two weeks in skin and may be very delayed in more slowly proliferating tissues.

TIME IN FRACTIONATED RADIOTHERAPY

By V. H. J. Svoboda

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To reduce the overall time of a course of daily fractionated radiotherapy from 21 to five, or from 30 to ten days, requires only 10% reduction of the dose for the same response if the number of fractions is preserved.

In the last three-and-a-half years, radiotherapy by three or more daily sessions has been used in patients with carcinoma of the breast, neck, lung and bladder.

Large area of the chest wall and breast tolerated 4250 rad of megavoltage X rays in 15 fractions and five days. Acute skin reaction was observed only when bolus or vaseline gauze was used. 4750 rad was similarly tolerated when delivered in 24 fractions and ten days. With larger fractions, fibrosis developed between six and 18 months. The skin reactions, tumour response and late changes were demonstrated by clinical photographs.

The whole larynx tolerates 5500 rad of megavoltage X rays in 24 fractions, ten days. This dose given in 34 fractions and 12 days produced the same reaction. The early tolerance of the lung to a variety of régimes and doses was good. 3500 rad in 15 fractions and five days to the pelvis before radical cystectomy produced only transient diarrhoea in the second week.

The tolerance of the normal tissues depended on the size and number of fractions and rose steeply up to 20 fractions. Further increase in the number of fractions produced only marginal improvement of the tolerance.

In several patients with multiple malignant skin lesions, a number of small and middle size fields were treated by 100 kV X rays. A variety of fractionations was used. Split dose reactions with 24- and three-hour intervals were indistinguishable. Similarly, three fractions of 820 rad led to the same reaction when delivered in three days or six hours. The same acute reaction was produced by 15 fractions of 270 rad in five days, as in 28 hours. Régimes, using 15–20 fractions and three–four daily sessions produced a 10% greater effect than the expected equivalent single exposures.

It was concluded that as with the megavoltage treatments approximately 95% of the 24 hours intracellular recovery occurred in less than three hours. The response of advanced tumours was at least as good as with conventional fractionation. In this way, the therapeutic ratio for some tumours could be improved.

Radiotherapy by multiple daily sessions is economical, because the total number of sessions is small, and only short hospitalization is needed. Preoperative treatment can be delivered within a few days, and the dose of adjuvant chemotherapy or a sensitizer could be reduced for a similar effect.

A COMPARATIVE TRIAL OF LARGE AND SMALL FRACTIONS

By J. M. Henk and K. W. James

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Optimum dose-time relationships in clinical radiotherapy remain controversial. There have been very few controlled trials comparing different fractionation schedules. The results of controlled trials of new methods of treatment are never widely accepted because of criticism of the dose and fractionation in the control arms of the trials. An example is the Cardiff trial of hyperbaric oxygen in head and neck cancer (Henk *et al.*, 1970), in which the control group was treated with ten fractions in 22 days to a tumour dose of between 3500 and 4500 rad depending on field size. Accordingly, this scheme was compared in a controlled trial with a 30-fraction six-week schedule, giving each group the same nominal standard dose. Patients admitted to the trial were suffering from advanced head and neck cancer, suitable for treatment by radical radiotherapy, but were unfit to enter the hyperbaric oxygen trial because of age or respiratory disease. Ninety-eight matched pairs were treated from 1971 to 1975. Acute mucosal reactions were more severe but healed more rapidly in the ten-fraction group; skin reactions were more severe and prolonged in the 30-fraction group. No difference between the two fractionation schedules in respect of tumour control or late normal tissue effects have so far been demonstrated. The therapeutic ratio appears to be the same, and the nominal standard dose formula seems correct over this range. Dose-response curves suggested that there was no difference in reoxygenation. It is concluded that the allegedly poor results in the control group of the Cardiff hyperbaric oxygen trial were not due to the small number of fractions used.

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Computerized axial tomography and echography as aids to radiotherapy planning

Chairman: Professor E. C. Easson

Diagnostic ultrasound in radiation therapy, by D. J. Brascho.
Radioisotope transverse section tomography as an aid to radiotherapy planning, by W. I. Keyes and I. J. Kerby.
The use of an ultrasonic scanner within the radiotherapy department, by P. C. Badcock and S. Leeman.
The staging of tumours using ultrasound, by Patricia Morley.
Ultrasonic scanning in radiotherapy planning of retroperitoneal masses, by C. J. Tyrrell and S. C. Lillicrap.

DIAGNOSTIC ULTRASOUND IN RADIATION THERAPY

By D. J. Brascho

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The successful management of cancer with high energy radiation requires precise knowledge of the tumour position relative to the body surface and normal organs. The author has developed the techniques of utilizing diagnostic ultrasound to determine the size and location of deep abdominal and pelvic tumours in patients undergoing radiation therapy. Radiation fields are established dynamically under direct ultrasound imaging, and anatomical information about the tumour and normal organs is entered directly into a computer programmed for radiation therapy planning. Diagnostic ultrasound is a safe, non-invasive technique of acquiring anatomical information that cannot be obtained by other diagnostic methods, and its application in clinical radiation therapy planning has the potential of improving cure rates and decreasing complication rates.

RADIOISOTOPE TRANSVERSE SECTION TOMOGRAPHY AS AN AID TO RADIOTHERAPY PLANNING

By W. I. Keyes and I. J. Kerby

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Practical experience is still based largely on brain section examinations. The main uses of the technique are summarized as, firstly, detection and to some extent characterization of lesions, and secondly, location of the lesion to indicate the volume to be treated if required. Thirdly, a hope for the future, the quantification of radioisotope uptake in tumour tissue may be useful. A section through the tumour effectively separates it from the surrounding tissues. Quantitatively accurate reconstructions of sections have been shown to be feasible. If radioisotope uptake such as Ga^{67} could be used to monitor the effect of radiotherapy or chemotherapy on tumours, transverse section tomography could prove extremely valuable.

THE USE OF AN ULTRASONIC SCANNER WITHIN THE RADIOTHERAPY DEPARTMENT

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Successful radiotherapy practice depends on irradiating tumours to a sufficiently high dose to cause their destruction whilst minimally damaging the surrounding normal tissues. Unfortunately the techniques for acquiring data on the patient's anatomy and tumour morphology have lagged behind progress made in calculating and administering localized high doses of irradiation. Apart from its use in the detection and staging of tumours, ultrasound scanning offers particular advantages in treatment planning, an application little developed so far.

In 400 patients at the Hammersmith Hospital, tumours in the following areas have been scanned—bladder, prostate, ovary, kidney, pancreas, retroperitoneal space, chest wall, thyroid gland, skin and underlying soft tissues. The technique has proved valuable and in many cases heavy reliance has been placed on the information obtained when more conventional investigation has not allowed imaging of the tumour in the plane of the radiotherapy fields with the patient in the treatment position. On occasions carefully planned treatments based on conventional planning procedures have had to be modified as ultrasound scans have revealed inadequate cover of the tumour or non-optimal treatment field positioning. It would seem advisable that the use of this technique, with its high patient acceptability, should be developed in the planning of radiotherapy treatments.

THE STAGING OF TUMOURS USING ULTRASOUND

By Patricia Morley

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A small group of patients with carcinoma of the uterine cervix and a larger group with bladder tumours have been scanned in an attempt to assess the value of ultrasound in pre-treatment clinical staging and in monitoring regression or local extension of the tumour after treatment.

With cervical carcinoma it is possible to demonstrate expansion of the cervix, parametrial invasion, spread up the pelvic side wall and bladder involvement. Patients clinically staged as IIIB and IV (with bladder invasion) could also be staged by the ultrasonic scan. However, changes in the pelvic echoes associated with IIB tumours proved more difficult to identify and could not be recognized in a significant proportion of cases. Locally recurrent tumour was defined in a small number of patients and in some it proved possible to differentiate tumour recurrence from post-irradiation fibrosis even though the diagnosis was not initially obvious on clinical examination.

The majority of bladder tumours are clearly demonstrated and their size and extent of invasion determined. Stages T1, T2, T3+ can be recognized from the appearance of the tumour and changes in the bladder wall and pelvic soft tissues. The overall accuracy of ultrasonic staging was 80% when compared with staging by conventional clinical methods. This compares favourably with most radiological methods of staging other than arteriographic techniques. A number of the tumours were treated by cystectomy, partial cystectomy or suprapubic diathermy; of this group the conventional method of staging the tumours was found to be more accurate with T1 tumours, whereas ultrasonic staging was more accurate with T2 and T3+ tumours. As well as the pre-treatment staging of bladder tumours ultrasound may be used to monitor the lesion after treatment and to detect early pelvic recurrence.

It is not suggested that ultrasound should replace established methods of clinical staging but that it is a useful examination in selected cases.

ULTRASONIC SCANNING IN RADIOTHERAPY PLANNING OF RETROPERITONEAL MASSES

By C. J. Tyrrell and S. C. Lillicrap

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Over 300 examinations of the retroperitoneal nodes have been performed using a custom-built grey scale ultrasonic scanner at the Royal Marsden Hospital. Sixty-three cases with involved nodes have been subsequently confirmed either at laparotomy, post-mortem examination, unequivocally positive lymphogram, or on clinical examination.

The importance of recognition of normal anatomy was stressed. The inferior vena cava and portal vein can be so close together as to simulate a mass, and may be incorrectly thought to be abnormal.

The importance of defining the limits of an abnormality in two planes, longitudinally as well as transversely, was also stressed, as were the advantages of single sector sweeps compared with compounded scans for improving definition.

Ultrasound is useful in radiotherapy planning in those areas where existing methods are inadequate. It is most useful in the para-aortic region:

(1) When a lymphogram is grossly abnormal the true extent of the mass may not be evident because of partial opacification (more common in solid tumours than lymphomas). The ureteric displacement on the intravenous pyelogram may also underestimate the lateral extent of the tumour mass.
(2) Grossly obstructed lymphatics from pelvic involvement when a lymphogram may show non-opacification in the para-aortic region.
(3) If a lymphogram is contra-indicated.

Porta hepatis and the lymph nodes outside the areas shown by lymphography may be visualized. Colonic recurrent masses and pancreatic primary tumours may be localized.

An opaque projector is used to enlarge the ultrasonic image to life size and information is transferred directly to treatment outlines. Using this information multiple field arrangements have been devised for the para-aortic nodes and for pancreatic tumours. These arrangements are only practical provided field length is not too great, that disease does not extend into psoas major between kidney and vertebral column, that disease does not extend inferior to the kidney and that the kidneys are not abnormally anteriorly situated making renal shielding impossible.

In addition to localization, ultrasound has proved useful for assessing response, checking ports and for follow-up.

Diagnostic/nuclear medicine session

Chairman: Dr. D. H. Trapnell

What use are radionuclides in renal disorders? by K. E. Britton and A. J. W. Hilson.
Pneumomediastinography in the diagnosis of mediastinal pathology, by M. D. Sumerling.
Radiology of the mediastinum, by M. Viamonte.

WHAT USE ARE RADIONUCLIDES IN RENAL DISORDERS?

By K. E. Britton and A. J. W. Hilson

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The primary use of radionuclides in renal disorders is to measure the contribution of each kidney to total renal function. By this means the amount of renal function that will be lost is known to the surgeon when he has to make a choice between nephrectomy and restorative operation, particularly in the context of renal calculus and hydronephrosis. This may be achieved by three-detector renography incorporating a tissue background subtraction system or by use of the gamma camera computer system allowing measurement of activity in regions of interest.

For the gamma camera system ^{99}Tc^{m} DTPA, an agent handled by glomerular filtration, allows visualization and measurement of uptake, the transit and removal of activity. These measurements enable the distinction to be made, for example, between acute tubular necrosis, which has a maximum parenchymal activity at two minutes falling by 30 minutes without visualization of the outflow system; and other causes of oliguria. Routine use in renal transplants has contributed to their management. Use of ^{99}Tc^{m} DMSA, which is taken up but not excreted, allows measurement of the distribution of the functioning renal mass in each kidney and the identification of space-occupying lesions in the parenchyme.

PNEUMOMEDIASTINOGRAPHY IN THE DIAGNOSIS OF MEDIASTINAL PATHOLOGY

By M. D. Sumerling

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The structures of the mediastinum may be outlined by the injection of gas through a fine needle introduced either by the retrotracheal or the transtracheal route. This is performed under local anaesthesia and with careful precautions no morbidity has been encountered in a series of 120 patients. 300–500 ml of gas (100 c.c. nitrous oxide followed by oxygen) injected into the mediastinum and followed by tomography in the frontal and lateral planes will display the anatomy. The superior vena cava, aorta and great vessels, pulmonary artery, right ventricular outflow tract, main pulmonary artery, trachea and main bronchi, left atrium, azygos vein, the thymus and lymphatic glands may be seen at the various levels of tomographic cuts. Examples of normal anatomy were shown.

Two cases with enlargement of the thymus were presented, the first in a patient with Hashimoto's disease and the second a patient with myasthenia gravis.

The value of the technique was illustrated by further cases. In two patients with reticulosis, the first a case of lymphosarcoma and the second a case of lymphadenoma, masses were well delineated by the technique. In one the enlarged glands were not visualized on conventional radiography. A young man with an unusual left border of the heart demonstrated on a routine X ray of the chest, complained of no symptoms, and the technique showed a well-delineated mass adjacent to the heart. This proved to be a pericardial cyst at operation. The final patient was an example of a case of mediastinal hyperparathyroid adenoma which was only demonstrated with confidence after diagnostic pneumomediastinography.

This technique has largely been replaced by mediastinoscopy. The latter technique, while giving histological confirmation has a definite morbidity. Although non-invasive techniques may become increasingly important, diagnostic pneumomediastinography may still play a useful part in the diagnosis of pathology in the mediastinum.

RADIOLOGY OF THE MEDIASTINUM

By M. Viamonte

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Horizontal, coronal and sagittal sections of cadavers have been the basis of our anatomical studies. As radiographic examinations are bi-dimensional representations of tri-dimensional structures, this background in anatomy is essential for the correct recognition of mediastinal abnormalities and to relate mediastinal pathology to specific organs. Practical observations derived from our anatomical studies are the following: the ascending aorta is a centrally placed organ. Pathology of the supravalvular portion of this vessel is difficult to recognize radiographically in view of the fact that it is not a border forming structure. Frontal, lateral, and obliques will miss subtle changes in the root of the aorta. The superior vena cava and the inferior vena cava both are anterior structures in their terminal portion. It is important to note that particularly in the abdomen, displacement of the inferior vena cava is related to enlargement of posterior structures while in the chest it is the consequence of enlargement of anteriorly located structures.

The position of the descending aorta to the left and slightly anterior to the thoracic vertebral bodies explains why aneurysms of this vessel can project to the left or to the right of the mediastinum. The pleural reflections and the medial projection of lung parenchyma explains why carcinomas of the lung may present as an anterior mediastinal mass and mimic a tumour arising from mediastinal structures. It also explains why it is possible to see the outline of posterior mediastinal structures due to the presence of air in the lung parenchyma surrounding these structures.

Tomography and barium studies are simple radiographic techniques which complement the information derived from conventional roentgenography. It is not so important to be precise in the histologic diagnosis of a mediastinal mass as it is to recognize its presence and to try to distinguish vascular from non-vascular processes. Angiocardiography, using the intravenous route (preferably injecting an antecubital vein) and azygography are excellent simple methods to establish the extent of a known neoplasm and assess its resectability. Ultrasound examination and imaging of the mediastinum with radionuclides as well as radionuclide angiocardiography may precede more elaborate diagnostic tests such as vascular studies. The radiological flow chart for assessing the mediastinum will be presented.

Proceedings of The British Institute of Radiology

New modalities in the treatment of cancer

Chairman: Mr. W. M. Ross

New modalities in radiotherapy: the perspectives, by J. F. Fowler.
Some observations on total body hyperthermia, by A. Mackenzie.
Experiences with cerebral hemisphere hyperthermia in the treatment of malignant gliomas, by B. Cummins and I. McIntosh.
Comparisons of the clinical effects of 7.5 MeV neutrons with those of photons, by Mary Catterall.
Treatment of carcinoma of the nasopharynx in hyperbaric oxygen: an outside assessment, by R. Sealy, R. J. Berry, R. Ryall, E. Mills and S. L. Sellars.
Progress of clinical trials of hyperbaric oxygen in head and neck cancer, by J. M. Henk.
Hypoxic cell sensitizers in clinical radiotherapy, by S. Dische.

NEW MODALITIES IN RADIOTHERAPY: THE PERSPECTIVES

By J. F. Fowler

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Prolongation of fractionation has the disadvantage that the tumour may outgrow the treatment but the advantage that adequate reoxygenation of hypoxic cells in tumours can occur. An optimum overall time is indeed seen in experimental C3H mouse tumours. At overall times shorter than the optimum, results are very variable and depend mainly upon the amount of reoxygenation that occurs. Better results were obtained for a greater number of smaller fractions, or for X rays plus hypoxic-cell radiosensitizers, or for fast neutrons. These new modalities may therefore make short fractionation schedules more reliable than hitherto. The interesting practical possibility is that short schedules, using an appropriate new technique, would reduce the overall time of treatment a patient has to endure. There are obvious economic implications.

The radiobiological and early clinical data were briefly reviewed and compared for the following "new" approaches:

1. Multiple fractions each day;
2. Hyperthermia, with or without X rays;
3. Ways of eliminating hypoxic cells in tumours:
    - (a) Hyperbaric oxygen;
    - (b) Fast neutrons or negative pions;
    - (c) Hypoxic-cell radiosensitizers (*e.g.* Ro–07–0582);
    - (d) Heavy ions such as accelerated neon nuclei;
4. Ways of improving physical dose distributions:
    - (a) Betatrons (*e.g.* Ault's results at Toronto);
    - (b) Negative pions;
    - (c) Protons.

Combinations of methods seem likely to be useful, such as protons plus hypoxic-cell radiosensitizers, or the use of hyperthermia to enhance the effects of certain cytotoxic drugs.

SOME OBSERVATIONS ON TOTAL BODY HYPERTHERMIA

By A. Mackenzie

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An extension of the methods used to rewarm hypothermic patients and to maintain normothermia in adverse environmental conditions makes it possible to induce controlled hyperthermia and to maintain the desired level of temperature with a considerable degree of accuracy. Using the same basic technique as that described by Henderson and Pettigrew (1971) total body temperature can be raised predictably and rapidly to 41.8°C with few unmanageable side effects. It is possible that temperatures in excess of this may give rise to disorders of liver function (Pettigrew *et al.*, 1974). If there is a place for total body hyperthermia in the treatment of cancer this technique offers a safe and rapid method of achieving it.

Currently animal experiments involving the pig are taking place in an attempt to define more accurately any ill effects of the hyperthermic state and to monitor temperature gradients throughout the body during the process. A simplified heating system utilizing an insulated heat cage together with warmed humidified gas to the lungs suffices for this work.

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HENDERSON, M. A., and PETTIGREW, R. T., 1971. Induction of controlled hyperthermia in treatment of cancer. *Lancet 1*, 1277.

PETTIGREW, R. T., GALT, JEAN M., LUDGATE, C. M., HORN, D. B., and SMITH, A. N., 1974. Circulatory and biochemical effects of whole body hyperthermia. *British Journal of Surgery, 61*, 727.

EXPERIENCES WITH CEREBRAL HEMISPHERE HYPERTHERMIA IN THE TREATMENT OF MALIGNANT GLIOMAS

By B. Cummins and I. McIntosh

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Malignant gliomas are rapidly lethal despite surgery, radiotherapy and chemotherapy. If they can be debulked the survival of the patient is prolonged. Usually peripheral spread of tumour invades vital areas of brain, precluding surgical excision. Gliomas very rarely metastasize.

We have devised a technique of local perfusion of the cerebral hemisphere containing the tumour, raising the temperature to 42°C over two hours. This has been used in five patients with inoperable malignant gliomas.

At the first stage, after biopsy confirmation of the malignancy of the tumour, a craniotomy is performed, the bone flap being removed and saved for replacement later. Two thermistors are placed in the tumour and one on the brain. A subdural pressure transducer and ventricular catheter are inserted. The patient is then monitored for three days.

At the second stage, under general anaesthesia, the carotid artery is cannulated, clamping off the external branch. A Xe^{133} blood flow study (CBF) is made as a control. The cannulae are linked to a cardiac pump and heat exchanger after anticoagulation of the patient. The minute volume of the bypass circuit is brought up in 50 ml/min steps until the control CBF level is reached. The carotid blood is then slowly heated until a tumour temperature of 42°C is attained. The heat exchanger temperature rarely exceeds 43°C, and haemolysis, though looked for every half hour, has not been a problem.

Continuous monitoring of the intratumour and brain temperature, intracranial pressure and blood pressure are logged on chart and tape. Continuous bilateral EEG records are taken throughout.

The tumour temperature is maintained at 42°C for two hours. The ipsilateral EEG usually becomes very abnormal during this stage but rapidly recovers on cooling.

Two patients died within 48 hours. One survived five months. Two patients survive ten and five months later, having achieved very considerable tumour lysis.

Hyperthermia may prove a useful adjunct to present therapy of malignant gliomas.

COMPARISONS OF THE CLINICAL EFFECTS OF 7.5 MeV NEUTRONS WITH THOSE OF PHOTONS

By Mary Catterall

Fast Neutron Clinic, M.R.C. Cyclotron Unit, Hammersmith Hospital, Du Cane Road, London W.12

Two of the five methods used to compare the clinical effects of high and low L.E.T. radiation were described. Firstly, the results of the controlled clinical trial of advanced tumours of the head and neck as reported by Catterall *et al.* (1975) have shown a statistically highly-significant benefit to the neutron-treated patients. This advantage was present in all sites and the floor of the mouth was taken as an example (Table I). Even where there were obvious lytic areas in the mandible due to tumour invasion, these have, so far, healed and there has, to date, been no necrosis of bone.

Two patients, each with two primary tumours, one treated with neutrons and the other with photons, were described. Skin scoring had shown that the intensity and duration of skin reaction (*i.e.* normal tissue damage) was the same in each treated area. In each patient both tumours had regressed equally and completely from clinical examination, but in both patients the photon treated tumour recurred, one at 24 and the other at 19 months. This suggested that, for an equal quantity of radiation, a qualitative difference was seen showing a clinical advantage to the neutron treated tumour.

REFERENCE

CATTERALL, M., SUTHERLAND, I., and BEWLEY, D. K., 1975. First results of a randomised clinical trial of fast neutrons compared with X or gamma rays in the treatment of advanced tumours of the head and neck. *British Medical Journal*, 2, 653–656.

TABLE I

CONTROLLED CLINICAL TRIAL. BUCCAL CAVITY

	Totals	Died within four months	Recurrence	Residual	Alive. No tumour	Alive > one year
Neutrons	21	4	0	2	9	8—No Rec.
Photons	22	5	7	7	2*	6—4 Rec.

*1 after surgical excision of recurrence; 1 other alive with tumour.

TREATMENT OF CARCINOMA OF THE NASOPHARYNX IN HYPERBARIC OXYGEN: AN OUTSIDE ASSESSMENT

By R. Sealy, R. J. Berry*, R. Ryall, E. Mills and S. L. Sellars

Departments of Radiotherapy and Otolaryngology, Groote Schuur Hospital and University of Cape Town Observatory, Cape, Republic of South Africa

The visit of one of the authors (R.J.B.) to the Groote Schuur Hospital, Cape Town, afforded an opportunity for independent peer review of the results obtained in treating patients with squamous carcinoma or lymphoepithelioma of the nasopharynx by irradiation, either in air using conventional dose-fractionation (usually 6000 R/30 fractions), or in hyperbaric oxygen (HBO) treating twice weekly with 4500 R/9 fractions. Forty-one of a total of 51 cases seen in the period 1966–73 were assessable and were followed up to three years. from the end of primary treatment or to death. Although at two years 38% (8/21) of the HBO treated patients were alive compared with only 18% (3/17) of the patients treated in air, neither the difference in survival nor in the death rate reached conventional statistical significance at the 5% level; for this nearly 150 patients would be required, a series impossible of achievement alone even in a large cancer centre. A higher proportion of patients in the air series died with recurrent or persistent local disease, whereas in the HBO group a higher proportion died with metastases. The same number of patients in each group died with peripheral recurrences, either in the central nervous system or the neck nodes, indicating the difficulty in assessing the spread of the tumour in locally advanced disease. The higher incidence of distant metastases in the HBO treated patients suggests that attention should be given to some form of systemic anti-cancer treatment following successful control of local disease.

PROGRESS OF CLINICAL TRIALS OF HYPERBARIC OXYGEN IN HEAD AND NECK CANCER

By J. M. Henk

Velindre Hospital, Cardiff

A controlled clinical trial in the radical radiotherapy of advanced head and neck cancer, begun in 1964, compared a ten-fraction three-week schedule in hyperbaric oxygen (HBO) with identical treatment in air. HBO produced a large and significant improvement in local tumour control but only a small increase in survival (Henk *et al.*, 1972).

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*On leave from M.R.C. Radiobiology Unit, Harwell, Didcot, Oxon.

Normal tissue effects were also increased in HBO. The trial therefore failed to show that HBO improves the therapeutic ratio, and it has also been criticized on the grounds that an "unorthodox" fractionation scheme was used in the control group. Accordingly a new trial began in 1972; the ten-fraction scheme in HBO was retained but with a 10% reduction in total dose to lower the complication rate; this was compared with a 30-fraction six-week schedule in air, the ret dose given to the air group being 10% higher than that given to the oxygen group. Ninety-three patients were admitted up to October 1975. The three-year actuarial survival rates are 61% in the HBO group and 35% in the air group ($p < 0.05$), the local tumour control rates at two years being 65% and 49% respectively. Late normal tissue effects are comparable so far in the two treatment groups. These trials suggest that the hypoxic tumour cell is a genuine problem in clinical radiotherapy, and that in the case of squamous carcinoma of the head and neck hyperbaric oxygen is more effective than fractionation alone in overcoming the oxygen effect.

REFERENCE

HENK, J. M., KUNKLER, P. B., and SMITH, C. W., 1972. Radiotherapy and hyperbaric oxygen in the treatment of head and neck carcinoma. *Proceedings of the 2nd A.E.R. Congress*, 319 (Excerpta Medica, Amsterdam.)

HYPOXIC CELL SENSITIZERS IN CLINICAL RADIOTHERAPY

By S. Dische

Regional Radiotherapy Centre,
Mount Vernon Hospital, Northwood, Middlesex

Radiobiological studies directed to developing hypoxic cell sensitizers began in 1963. They reached an important stage in 1973 when metronidazole gave promise of being an effective drug for clinical practice. Shortly afterwards another nitro-imidazole, a Roche experimental drug Ro–07–0582, was found to be more effective as a radiosensitizer. Clinical work commenced with metronidazole in 1973 and in 1974 with Ro–07–0582.

Metronidazole has to be given in very high dosage, compared with its use as a trichomonocide, if we are to achieve serum levels similar to those obtained in animals when radiosensitization was achieved. Doses from ten to 12 g have been given and this involves the administration of 40 to 48, 250 mg tablets. Nausea and vomiting does occur but the drug seems otherwise well tolerated; using nine doses over a three-week period, as employed by Urtasun in Edmonton, no other harmful effects have been observed. Urtasun (unpublished) has analysed a controlled trial of the treatment of gliomas and has shown statistically significant improvement in the duration of survival in those patients given metronidazole.

An initial study using single doses of Ro–07–0582 has now been completed at Mount Vernon (Gray *et al.*, 1976; Dische and Zanelli, 1976; Dische *et al.*, 1976; and Thomlinson *et al.*, 1976). It has been shown to be quite well tolerated and a study of skin reaction has shown that it is a highly effective sensitizer of hypoxic cells. It is three to four times more effective than metronidazole. In three of seven patients with multiple deposits of tumour there was evidence of an increased radiation effect in those treated when R0–07–0582 was administered.

Work is now proceeding with the administration of multiple doses of Ro–07–0582. Gastrointestinal side effects have not occurred nor has there been any evidence for a reduction of serum levels due to enzyme induction. However, neurotoxicity is proving to be a problem. We hope to develop a safe régime for use of this promising hypoxic cell sensitizer.

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GRAY, A. J., DISCHE, S., ADAMS, G. E., FLOCKHART, I. R., and FOSTER, J. L., 1976. Clinical testing of the radiosensitizer Ro–07–0582. I. Dose, tolerance, serum and tumour concentrations. *Clinical Radiology*, *27*, 151–157.

DISCHE, S., and ZANELLI, G. D., 1976. Skin reaction—A quantitative system for measurement of radiosensitization in man. *Clinical Radiology*, *27*, 145–149.

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THOMLINSON, R. H., DISCHE, S., GRAY, A. J., and ERRINGTON, L. M., 1976. Clinical testing of the radiosensitizer Ro–07–0582. III. Response of tumours. *Clinical Radiology*, *27*, 167–174.

Membership Subscription Reminder

Members of The British Institute of Radiology are reminded that their membership subscriptions become due on January 1, 1977, as follows:

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Cheques should be made payable to British Institute of Radiology, crossed and sent to the General Secretary, BIR, 32 Welbeck Street, London W1M 7PG.

1976, *British Journal of Radiology*, *49*, 1062

Forthcoming events and other notices

The Editors have decided that owing to the extreme shortage of space in *The British Journal of Radiology*, the "Forthcoming events and other notices" section will in future only carry notices of general interest and announcements of meetings specifically connected with The British Institute of Radiology and its associated bodies. Members, however, will be receiving future meeting announcements, space permitting, in the *BIR BULLETIN* which is distributed quarterly to all members.

Proliferation Kinetics

An all-day meeting organized by the Radiobiology Committee of The British Institute of Radiology, to be held on December 4, 1976. Further information from the General Secretary, The British Institute of Radiology.

British Medical Ultrasonics Group

The Annual Meeting of the British Medical Ultrasonics Group will be held at the University of Dundee on December 20–21, 1976.

Papers will be presented on all aspects of diagnostic ultrasound and there will be an associated commercial exhibition.

Further details and registration from: The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Effects of High LET Radiations

A radiobiology meeting to be held on January 21, 1977 at the B.I.R. Institute House, 32 Welbeck Street, London W1M 7PG. Further information from the General Secretary.

Radiology in the European Economic Community

A joint meeting organized by the Royal Society of Medicine (Section of Radiology) and the Royal College of Radiologists, to be held at the Royal Society of Medicine, London W1, on January 21, 1977. Details from the Royal College of Radiologists, 28 Portland Place, London W1.

Radioisotope Investigations of Diseases Involving the Endocrine Organs

An all-day meeting held jointly with the Endocrinology Society and organized by the Nuclear Medicine Committee of The British Institute of Radiology, to be held on February 16, 1977 at the Middlesex Hospital Medical School, London, W1. Registration details and further information from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Unorthodox Approaches to Fractionation

A meeting held jointly with the Royal College of Radiologists and the Royal Society of Medicine (Section of Radiology) on February 18, 1977. Information from the General Secretary, The British Institute of Radiology.

The British Institute of Radiology Annual Congress and Scientific Exhibition

To be held on April 14–15, 1977 at the R.I.B.A., London W1. Papers presented will include the "Silvanus Thompson Memorial Lecture" by Mr. G. N. Hounsfield, C.B.E., of EMI Central Research Laboratories.

Further information and registration from the General Secretary, The British Institute of Radiology, 32 Welbeck Street, London W1M 7PG.

Radiation Protection: An Example of Action Against Modern Hazards

The I.R.P.A. is organizing its 4th International Congress at the Paris Convention Centre from April 24–30, 1977.

The theme will cover scientific, health and technological aspects, protection of workers and protection of the public and the environment.

For further information please contact M. G. Bresson, Secrétaire-Général du IVème Congres International de l'I.R.P.A., B.P., no. 33, 92260 Fontenay-aux-Roses, France.

The Mackenzie Davidson Memorial Lecture

To be given by Dr. David Ingvar, University of Lund on May 19, 1977 at The British Institute of Radiology.

New Horizons in Intensifying Screen Technology

An all-day meeting organized by the Industry Committee of The British Institute of Radiology on May 20, 1977 at the Middlesex Hospital Medical School, London W1. Registration details and information from the General Secretary, The British Institute of Radiology.

Use of Krypton Generators

An all-day meeting organized by the Nuclear Medicine Committee of The British Institute of Radiology to be held at the Middlesex Hospital Medical School, London, W1 on June 15, 1977. Registration and details from the General Secretary.

Hypoxic Cell Sensitizers in Radiobiology and Radiotherapy

The 8th L. H. Gray Conference will be held in St. Catherine's College, Cambridge, on September 5–9, 1977, and will discuss subjects ranging from basic mechanisms of hypoxic cell sensitizers to clinical applications of these agents.

Further information may be obtained from Dr. G. E. Adams, C.R.C. Gray Laboratory, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN.

XIV International Congress of Radiology

To be held in Rio de Janeiro from October 23 to October 29, 1977.

Further information from XIV° Congresso Internacional de Radiologia, Patrocínio Colegio Brasileiro de Radiologia, Rio de Janeiro, Brasil.

Book reviews

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Erratum

It should be noted that the new publication reviewed on page 902, British Journal of Radiology, November 1976 should be entitled "*Journal de Neuroradiologie*".

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